Designing Adaptive Programs for Neuropathic Pain

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DIA 2011
Chicago, Illinois
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Acknowledgement

For outstanding programming support

Jaydeep Bhattacharya,

Cytel, Inc.

Outline

- Overview
- Statistical Models
  - Ph 2b and dose selection
  - Ph 3 design and Prob. of Success
- Commercial Model
  - Utility and 5th year Net Revenue
  - Cash flows and Net Present Value
- Simulation Results for a typical Ph2b+Ph3 program
  - Optimizing Ph2b Sample Size
  - Comparing Dose selection methods
  - Optimizing Ph2b and Ph3 sample sizes
  - Sensitivity to Dose Response Curves for Efficacy
- Summary
- Concluding Remarks

Overview

- First stage of a work-in-progress
- Optimize Ph2b sample size, dose selection method, and Ph3 sample size in a PH2b+Ph3 development program for Neuropathic Pain
- Outcome assessed *at program level* by number of patients required, Probability of Success (PoS) and profit
  - PoS measured by probability of two pivotal Ph3 trials demonstrating statistically significant drug efficacy compared to placebo
  - Profit measured by E(NPV). NPV determined by relationship of efficacy and tolerability profile of marketed dose to typical profits of comparator drugs and trial costs.

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Efficacy and Safety Response

- 0-10 pain scale used to measure efficacy for treatment of neuropathic pain in both Ph2 (12 wks.) and Ph3 (12 months)
  - Target level of efficacy (mean difference from placebo) = 1 unit
  - SD of efficacy response in Ph2 and Ph3 = 2 units
  - Mean Dose Response is 4-Parameter Logistic (4PL) function
  - Ph2 prior chosen to be practically flat over likely range of parameters of 4PL dose response
- Two types of AE's:
  - 'nuisance' AE's: non-transient, not manageable by other means (e.g. weight gain, sexual function AE's) but tolerable to different degrees by patients
  - serious AE's with rare probability of occurrence detectable only in the post marketing stage (e.g. CV events, liver failure). These are 'show-stoppers' so all estimates of profits are conditional on non-occurrence of serious AE's

Nuisance AE's

- Moderate probability of occurrence
  - will not cause stoppage of development or drug approval, but will lower the benefit/risk profile and negatively impact sales.
- Placebo nuisance AE rate= 0.1
- Drug nuisance AE rate
  - assumed similar to existing products on market (0.2 to 0.3)
  - For low doses = 0.1
  - For highest dose = 0.35

- Ph2 simulations
  - Binomial sampling from above rates.
  - Estimate AE rates at each dose using isotonic regression

Ph2b and PH 3 Designs

- For each replicated Ph2b trial MCMC samples from posterior distribution used to estimate mean responses at placebo and doses for efficacy and nuisance AE's
- Two methods to select dose, d_i at the end of Ph2b trial to take into Ph 3 trials
  - Dose estimated to be **closest to target efficacy**
  - Dose estimated to have **maximum utility (function of both efficacy and nuisance AE rate)**
- If no dose meets target difference from pbo, no Ph3 trials are conducted. If at least one dose meets target, run two concurrent Ph 3 trials each with sample size for 95% power (alpha=0.025, 1-sided)

ICH E1A guidance

- ICH E1A guidance for long term safety applicable for neuropathic pain (among others) is to have:
  - 1500 patients treated at the dose of interest, with at least 500 treated for ≥ 6 months and at least 100 for ≥ 1 yr.
  - Minimum required can be met by pooling Ph2 and Ph3 data with other unblinded studies.

Model for compliance with ICH E1A guidance

- We assume that Ph2 subjects on study drug are switched to the Ph3 dose and pbo subjects are continued on pbo for the Ph 3 treatment period of 12 months for safety assessment.
- We adjust Ph 3 sample sizes to follow this regulatory guidance assuming no other studies will be conducted. In every case we have considered this adjustment results in Ph3 being over-powered for efficacy.
- In practice this number can be lower or exposure time can be reduced in discussions with regulators where there is relevant experience (e.g. with other drugs having similar mechanisms of action, animal studies)

Calculating PoS and E(NPV)

- For each simulated Ph2b trial where a dose was selected to carry into Ph3 trials:
  - Analytically calculate predictive PoS = Pr(Both Ph3 trials show significance) using Normal priors for Ph3 trials with mean and SD of Ph2b posterior distribution.
  - Use this probability to calculate E(NPV) for the simulated Ph2b trial by combining
    - NPV calculated from Commercial model when there is Success
    - Negative NPV calculated from Ph2b and Ph3 trial costs when there is No Success
- Estimate E(NPV) by averaging over all Ph2b simulated trials

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Model for 5th Year Net Revenue/Utility

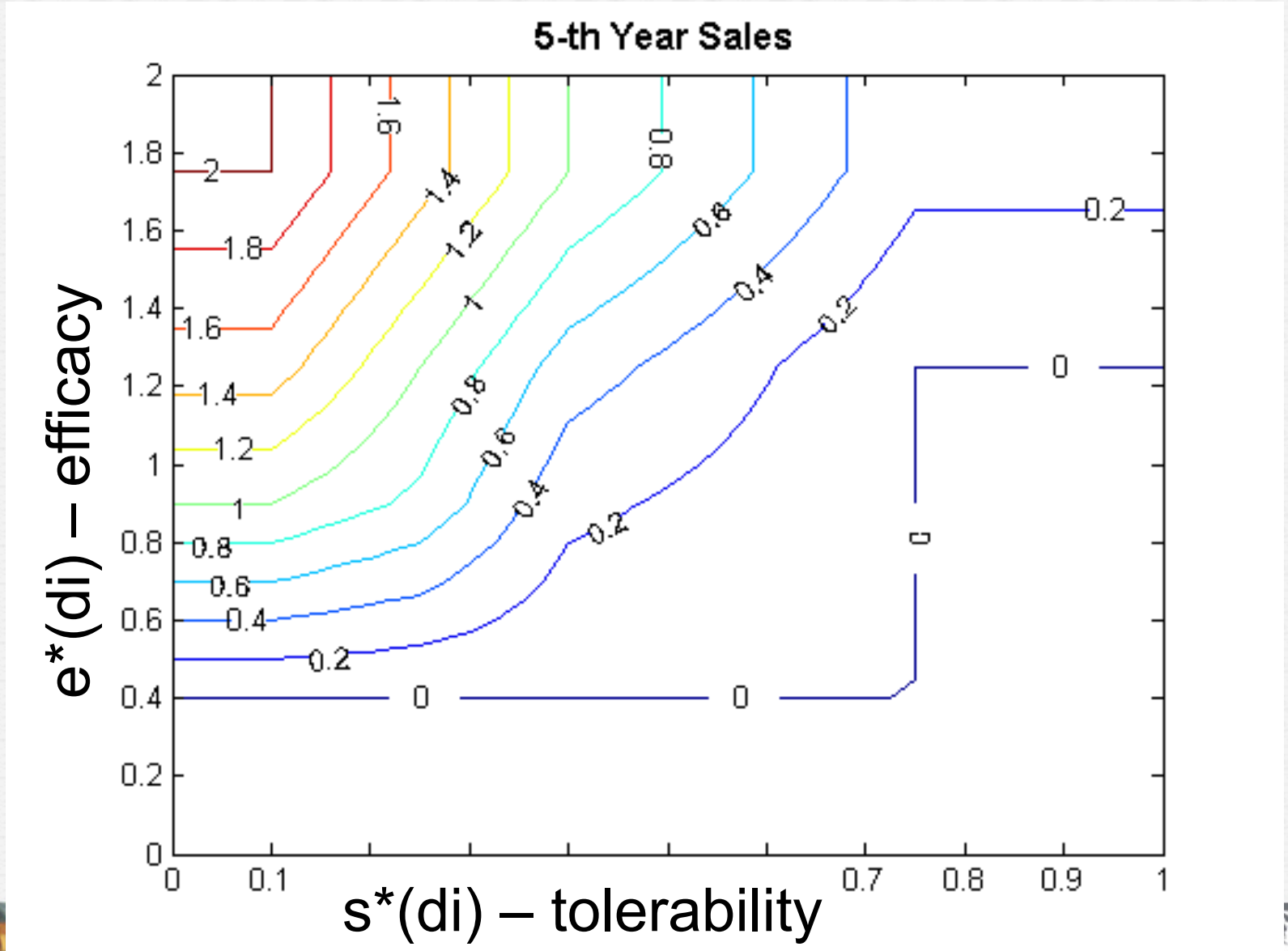
- Let $e^*(d_i)$ denote the true mean diff. in efficacy from pbo for dose d_i
  Let $s^*(d_i)$ denote the true nuisance AE rate (tolerability) for dose d_i
- Table shows fifth year net revenue ($B) from marketing a single dose that reflect trade-offs between efficacy and tolerability based on discussions with David Hewitt, MD, and Arnold Gammaitoni, MD who are clinical development experts in neuropathic pain.

5th Year Net Revenue ($B)

$e^*(di)/s^*(di)$	0	0.1	0.25	0.4	0.75	1
0	0	0	0	0	0	0
0.4	0	0	0	0	0	0
0.9	1	1	0.75	0.25	0	0
1.25	1.5	1.5	1	0.5	0	0
1.75	2	2	1.5	1	0.25	0.25
2	2	2	1.5	1	0.25	0.25

These values can be interpreted as **utility** of a dose in the market as utility functions have arbitrary origin and scale

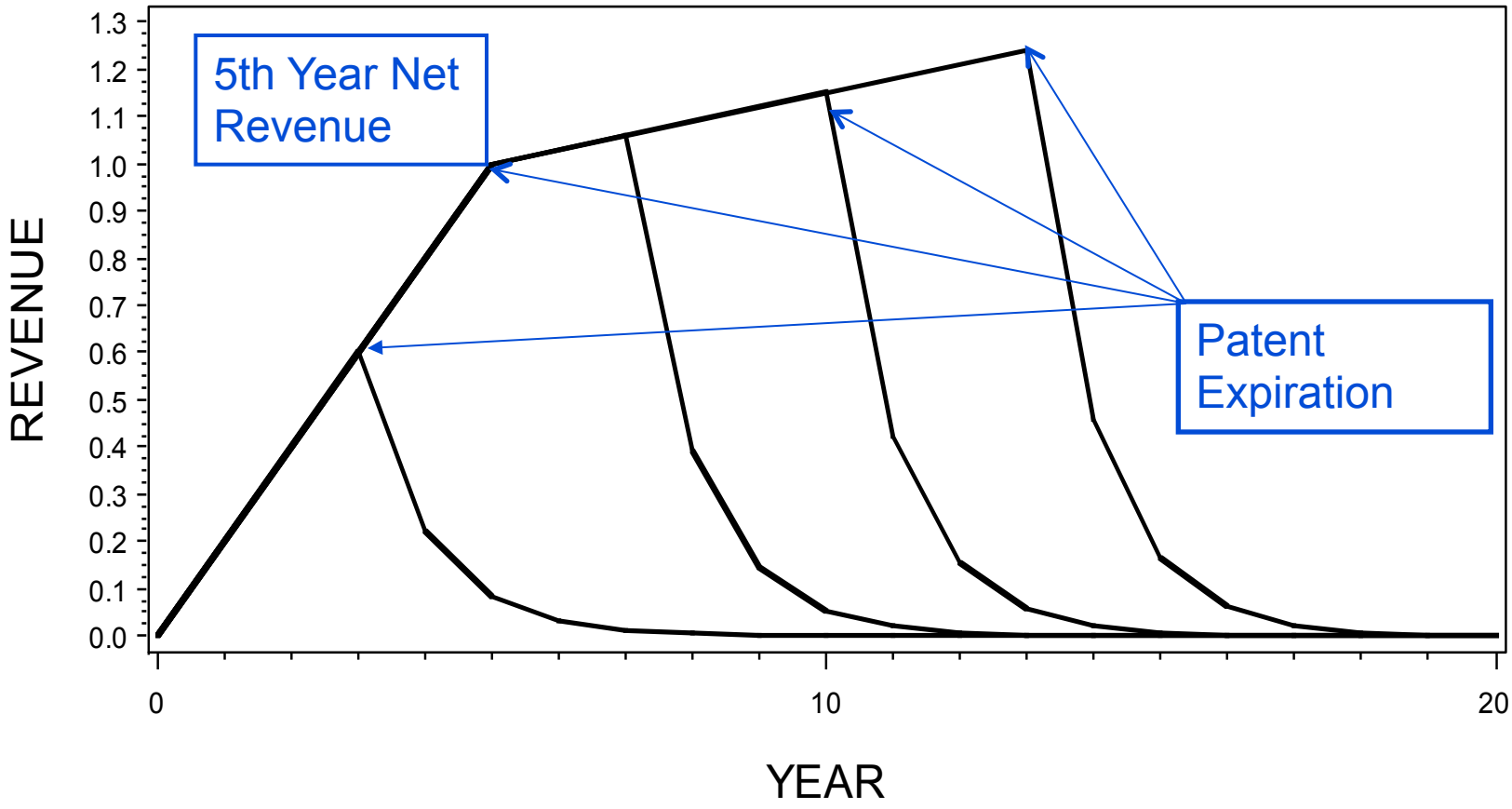
5th Year Net Revenue ($B)



Time Profile of Net Revenue

Slope after 5th year = b, Decay parameter for period after patent expiration = c

Revenue over time for Effective Patent Life TP=3,7,10,13
(S5=$1B, b=0.03, c=1)



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Base Case

Efficacy and Tolerability Dose Response

DRCurve	D0	D1	D2	D3	D4	D5	D6	D7	D8
Efficacy	0.000	0.001	0.034	0.217	0.567	0.854	1.002	1.068	1.099
Tolerability (Rate for Nuisance AE's)	0.10	0.10	0.10	0.10	0.15	0.20	0.25	0.30	0.35

Ph2 Sample Size = 30x9 = 270 subjects

simulations of Ph2 trial = 500

Time and Cost Estimates

Total patent life	17yrs.
Duration of Dev. Time before the Ph2b trial	2yrs.
Patient Accrual per month per site in Ph2b trial	0.5
# Sites in Ph2b trial	50
Lag between end Ph2b trial and start Ph3 trial	6 mo.
Patient Accrual per mo. per site in Ph3 trial	1
# Sites in each Ph3 trial	80
Duration between end of Ph3 trials and launch	12 mo.

Cost per site	$15K
Cost per patient	$3.5K
Start-up Cost of manufacturing and marketing	$1M
Revenue model parameter b	0.1
Revenue model parameter c	0.5
Discount rate per year	10%
Minimum # patients in Ph2b & Ph3 trials for compliance with ICH Safety guidance on Selected Dose	1500
Ph2b subjects completing long-term extension for compliance with ICH guidance	50%

Optimizing Ph2b Sample Size (selecting dose closest to target efficacy)

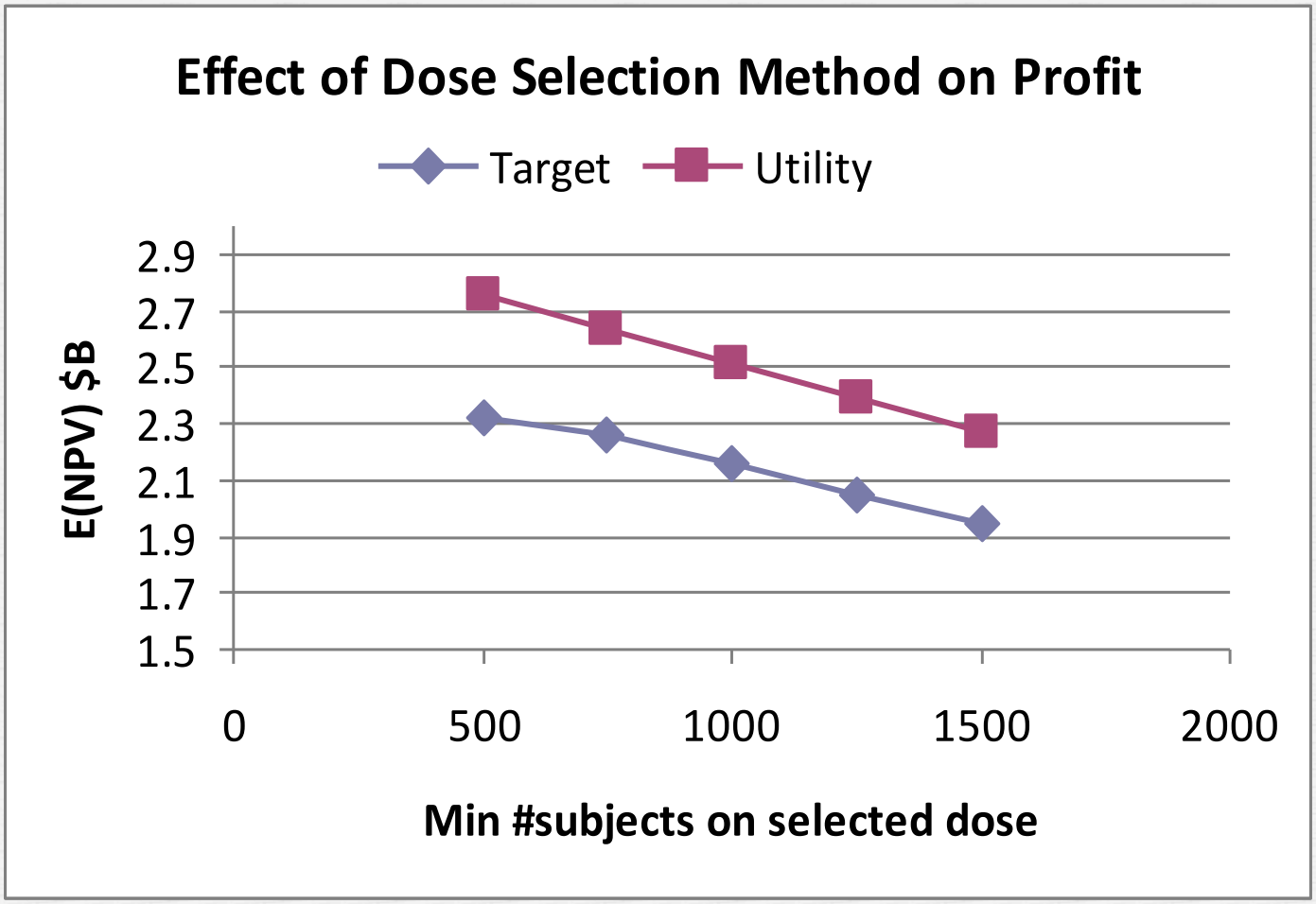
Phase 2 Sample size	Phase 2 Power	Prob. of going to Phase 3	Phase 3 Sample size (both trials)	Prob. Phase 3 Success	Total Development Time (yrs)	Expected True Discounted NPV ($B)
135 (=15x9)	0.82	0.75	2880	0.74	6.7	1.81
225 (=25x9)	0.95	0.79	2800	0.79	7.0	1.90
270 (=30x9)	0.97	0.80	2760	0.80	7.1	1.95
405 (=45x9)	0.99	0.84	2640	0.83	7.5	1.84
540 (=60x9)	0.99	0.87	2520	0.86	7.9	1.81

Highest PoS in Ph3 might not mean highest NPV

Comparison of Dose Selection Methods

	Prob. of going to Phase 3		Prob. Ph3 Success		Expected NPV ($B)		Improvement
Ph 2 Sample Size	Target Dose	Max Utility Dose.	Target Dose	Max Utility Dose.	Target Dose	Max Utility Dose.	%
135	0.75	0.82	0.74	0.82	1.81	2.04	13%
225	0.79	0.95	0.79	0.95	1.90	2.29	21%
270	0.80	0.97	0.80	0.97	1.95	2.27	16%
405	0.84	0.99	0.83	0.99	1.84	2.21	20%
540	0.87	0.99	0.86	0.99	1.81	2.10	16%

Reducing min # subjects in ICH guidance



Optimizing Ph 2 and Ph 3 Sample Sizes (with no minimum requirement for ICH guidance)

Optimizing Ph2 and Ph3 Sample Sizes	Optimum E(NPV)	Opt Ph2 Smpl Size	Opt Ph3 Smpl Size
Target Efficacy Dose	2.32	270	800
Max. Utility Dose	**2.80**	270	700

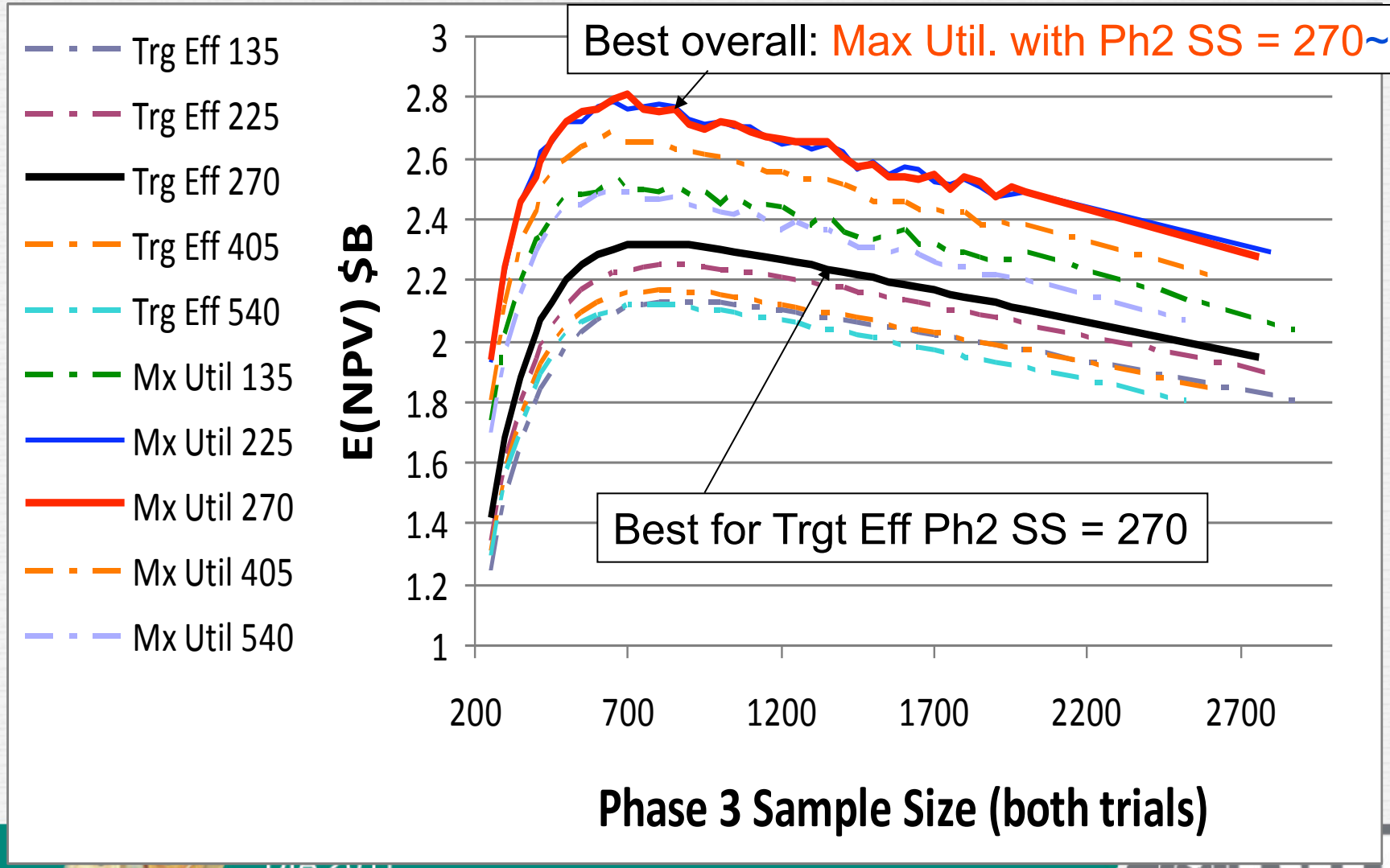
For optimal sample sizes:

Ph 2 power = 0.97

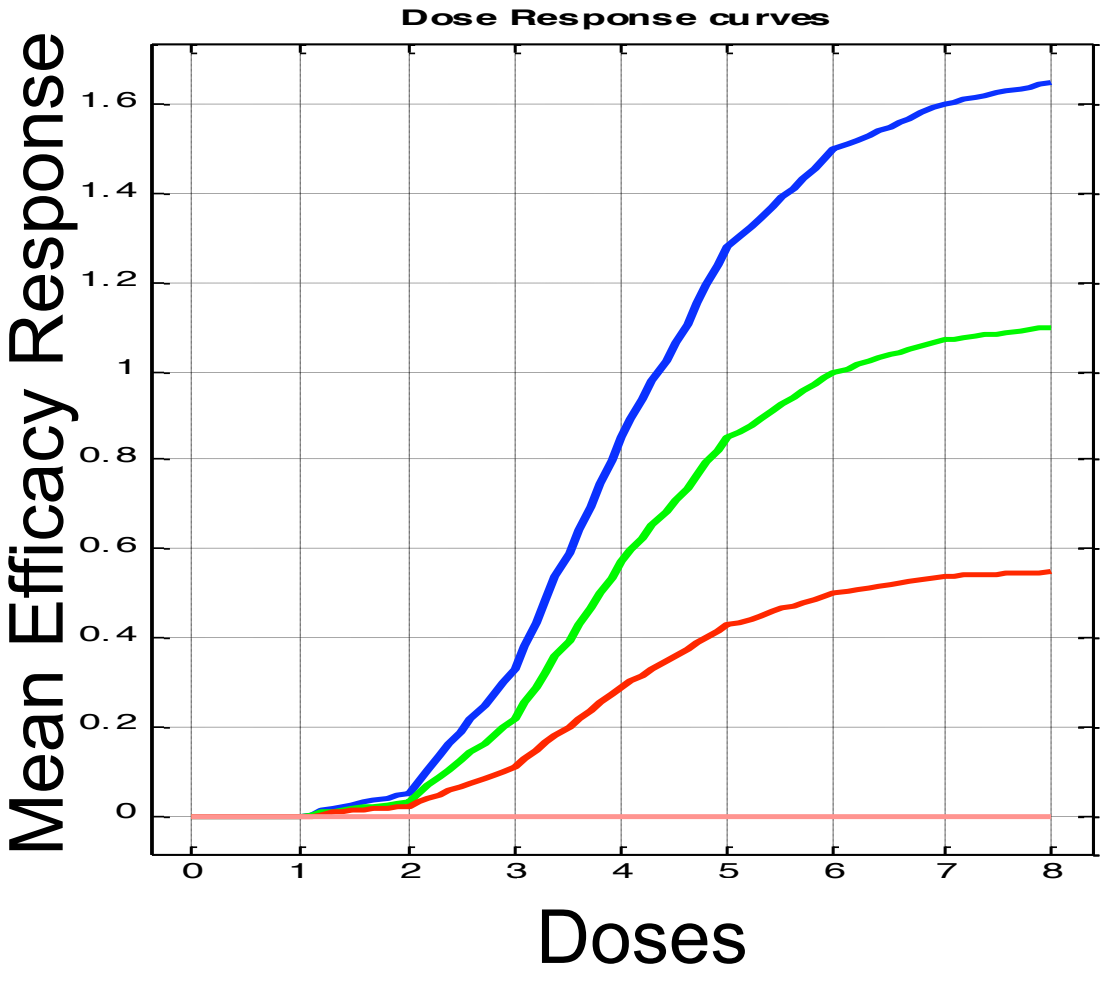
Ph3 power = 0.999 (Smpl Size= 800)

= 0.997 (Smpl Size =700)

Optimizing Ph 2 and Ph 3 Sample Sizes (no ICH guidance minimum)



Possible Dose Response Curves



1.5 x Eff. Case

Eff. (Base Case)

0.5 x Eff. Case

Zero Eff. Case

Sensitivity to Dose Response Curve

Max Utility dose selection

Dose Response Curve	Optimum Ph2b			Ph2 SSz =270			Ph2 Sample Size =225		
	Optimum Sample Size	Prob of Ph3 Success	Expected NPV ($B)	Prob of Ph3 Success	Expected NPV ($B)	Reduction from Optimum E(NPV)	Prob of Ph3 Success	Expected NPV ($B)	Reduction from Optimum E(NPV)
Flat Eff	135	0.00	**0.00**	0.00	**0.00**	-	0.00	**0.00**	-
0.5*Eff	540	0.77	**0.31**	0.55	**0.26**	16.42%	0.46	**0.21**	29.80%
Eff	225	0.95	**2.29**	0.97	**2.27**	0.87%	0.95	**2.29**	0.00%
1.5*Eff	135	0.99	**4.18**	1.00	**3.99**	4.51%	1.00	**4.05**	3.17%

Summary

- We have developed models and simulation tools to **optimize Ph2b and Ph3 designs** for Neuropathic Pain to maximize the commercial value of a typical Ph2b+Ph3 program.
- We have used this approach to show that:
  - **dose selection is substantially improved by using a utility function**
  - **increasing Ph3 sample sizes to meet ICH 1A safety guidance can have a large impact** on the commercial value of a program for Neuropathic Pain,
  - **the optimum Ph2 sample size is fairly robust** with respect to departure from assumptions of the dose response curve.

Concluding Remarks

Next steps will extend modeling & simulation tools to:

1. Carry two or more doses into Ph3. Select best Ph3 design adaptively based on Ph 2 results. Optimally design Ph 2 using preposterior analysis
2. Compare effect of having 4 doses (instead of 8) in Ph2b trial
3. Evaluate adaptive designs for Ph2
4. Evaluate group sequential designs for Ph 3
5. Use prior for probability of different dose response scenarios
6. Model uncertainty in 5th year sales forecast and recognize down-side risk by using measures other than E(NPV) to compare programs (e.g. probability of meeting a specified target level of NPV)

Thank you!

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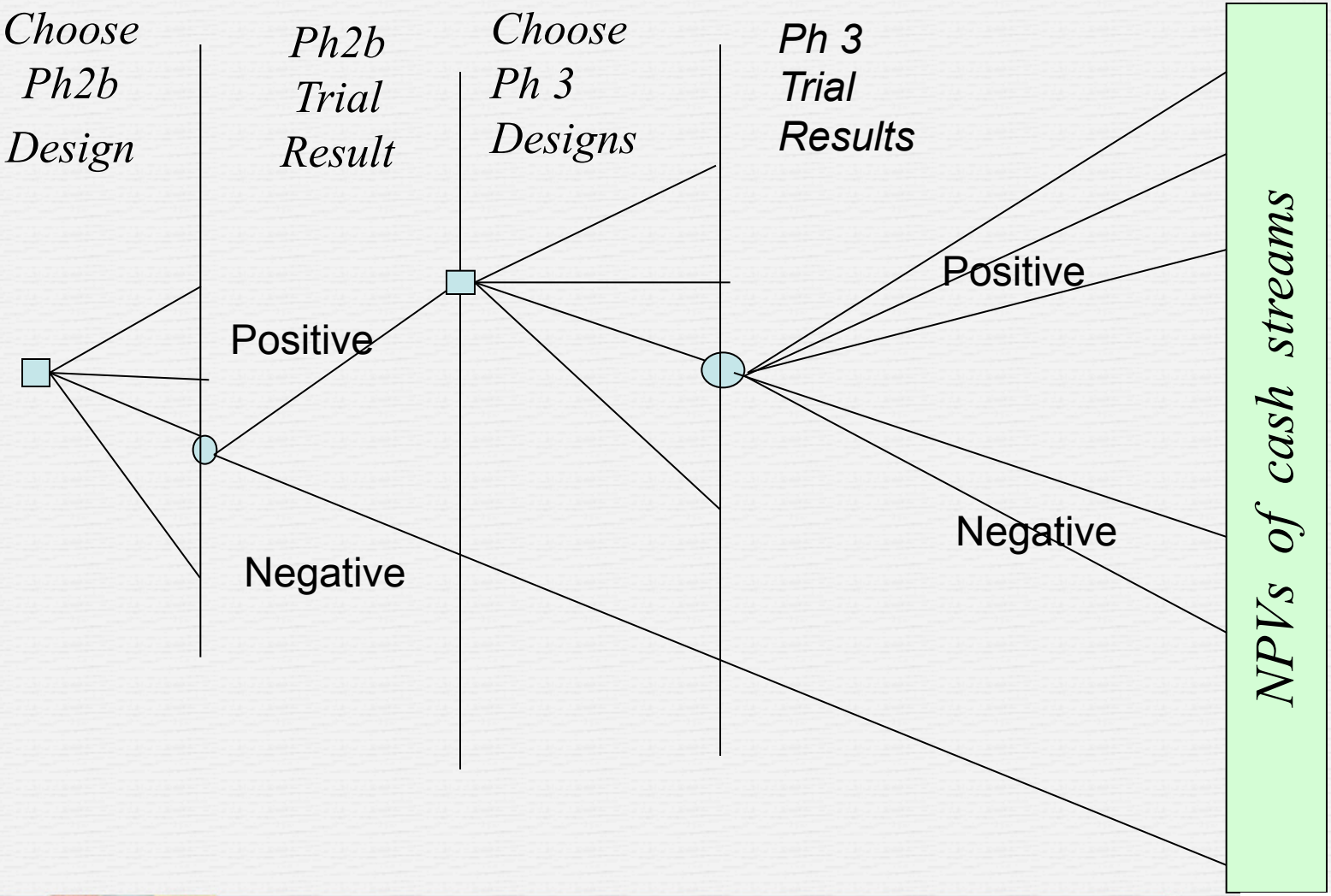
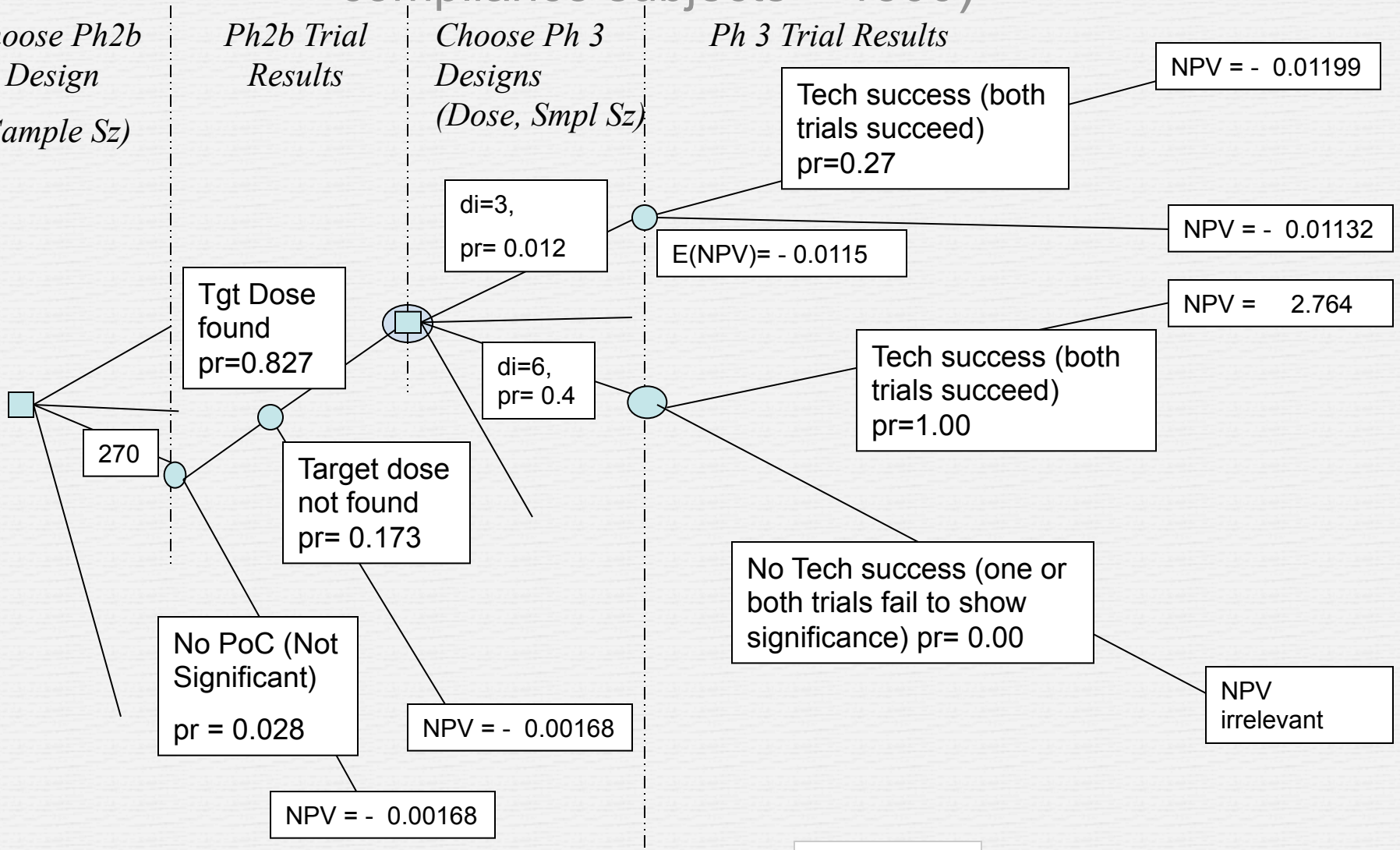
Extra Slides

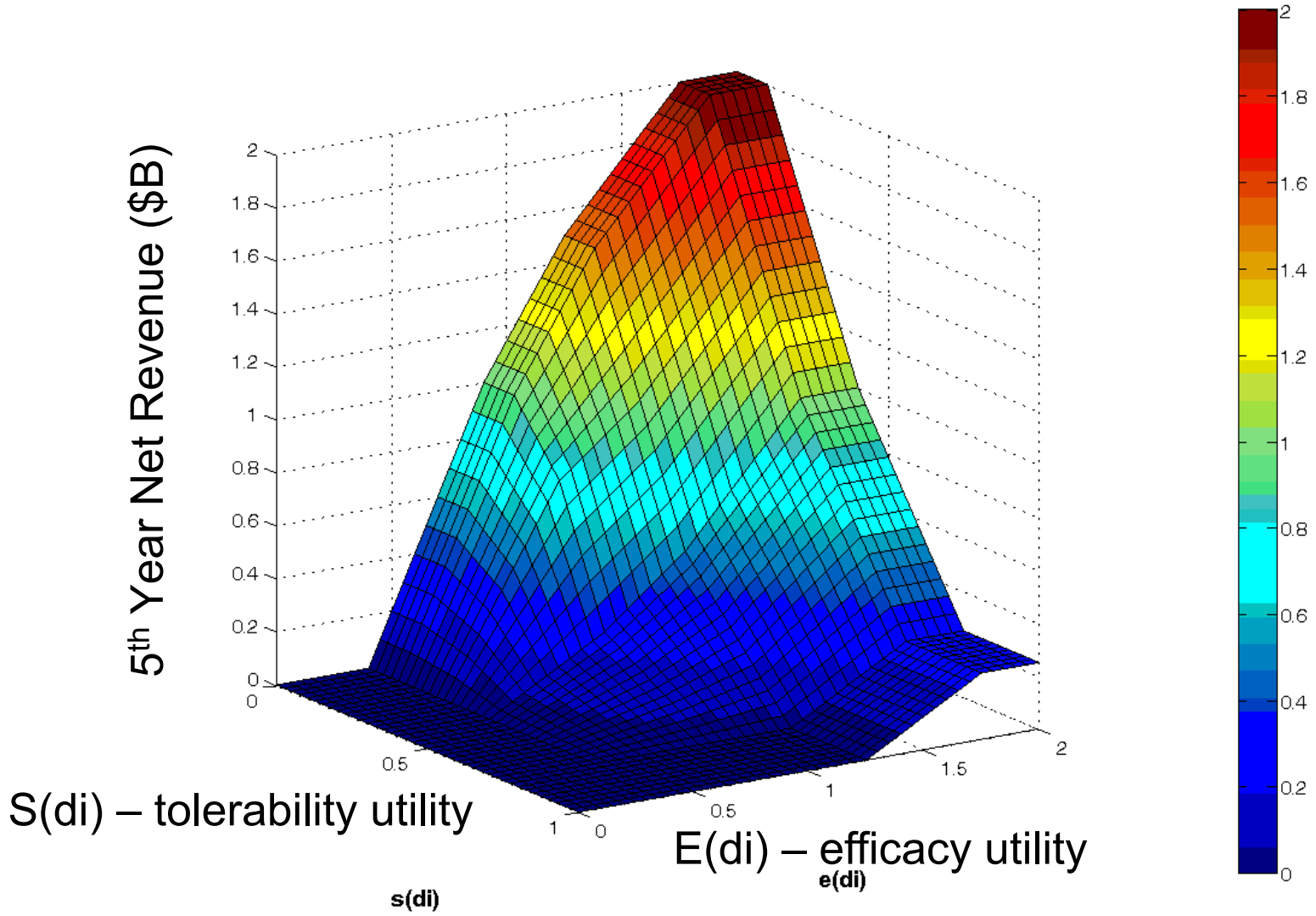
Decision Analysis Tree



Decision Tree (Base Case, "Efficacy" DRCurve, ICRH compliance subjects =1500)

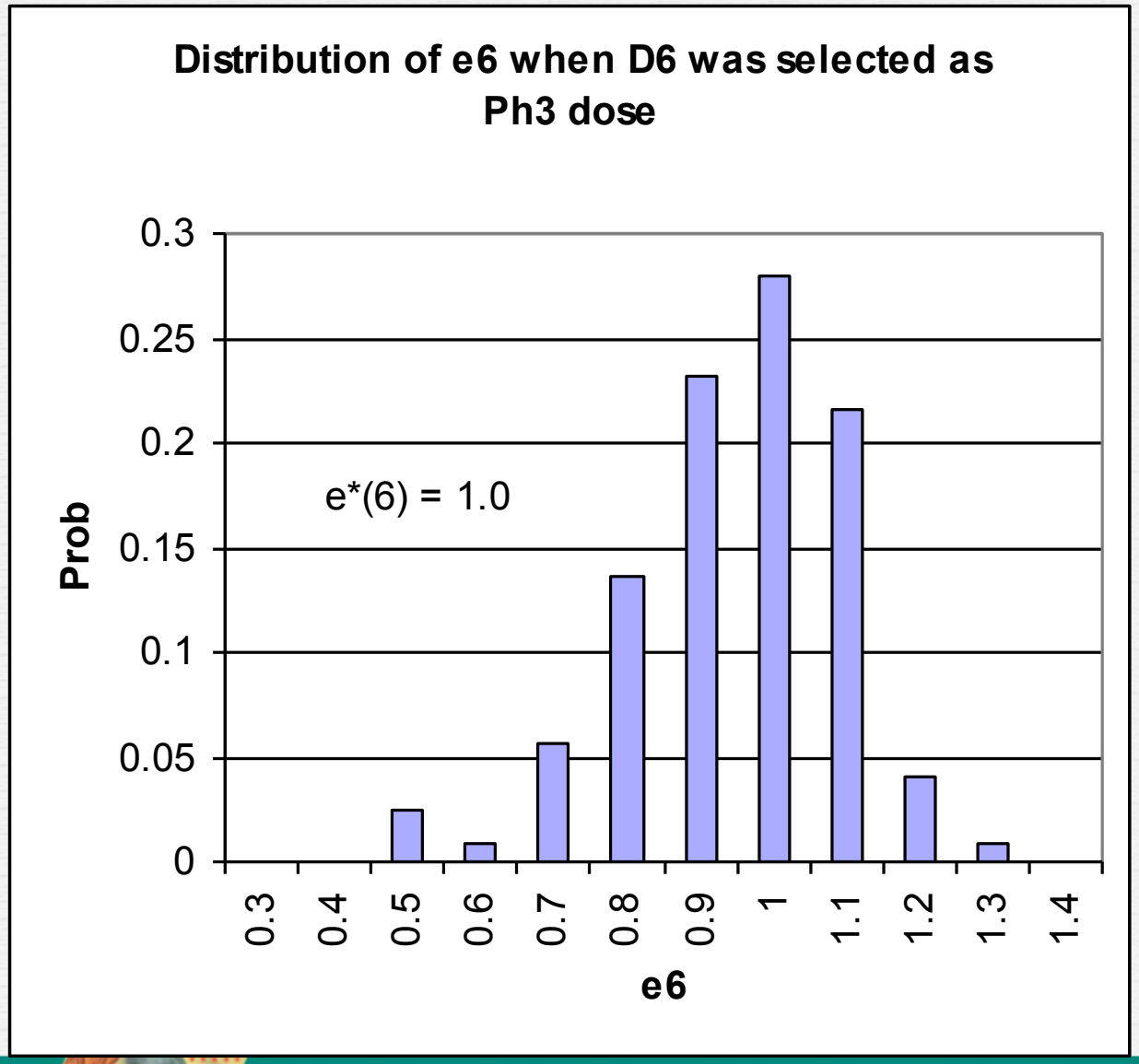


5th Year Net Revenue ($B)



Base Case (Efficacy DRCurve)

No dose selected	0.196
Dose selected	0.804
Pr(NoSignif)=	0.028
Pr(NoDoseSel|Signif)=	0.173
Pr(Dose Found|Signif)=	0.827
Pr(di =1|dose found)=	0.000
Pr(di =2|dose found)=	0.000
Pr(di =3|dose found)=	0.012
Pr(di =4|dose found)=	0.085
Pr(di =5|dose found)=	0.303
Pr(di =6|dose found)=	0.400
Pr(di =7|dose found)=	0.182
Pr(di =8|dose found)=	0.017



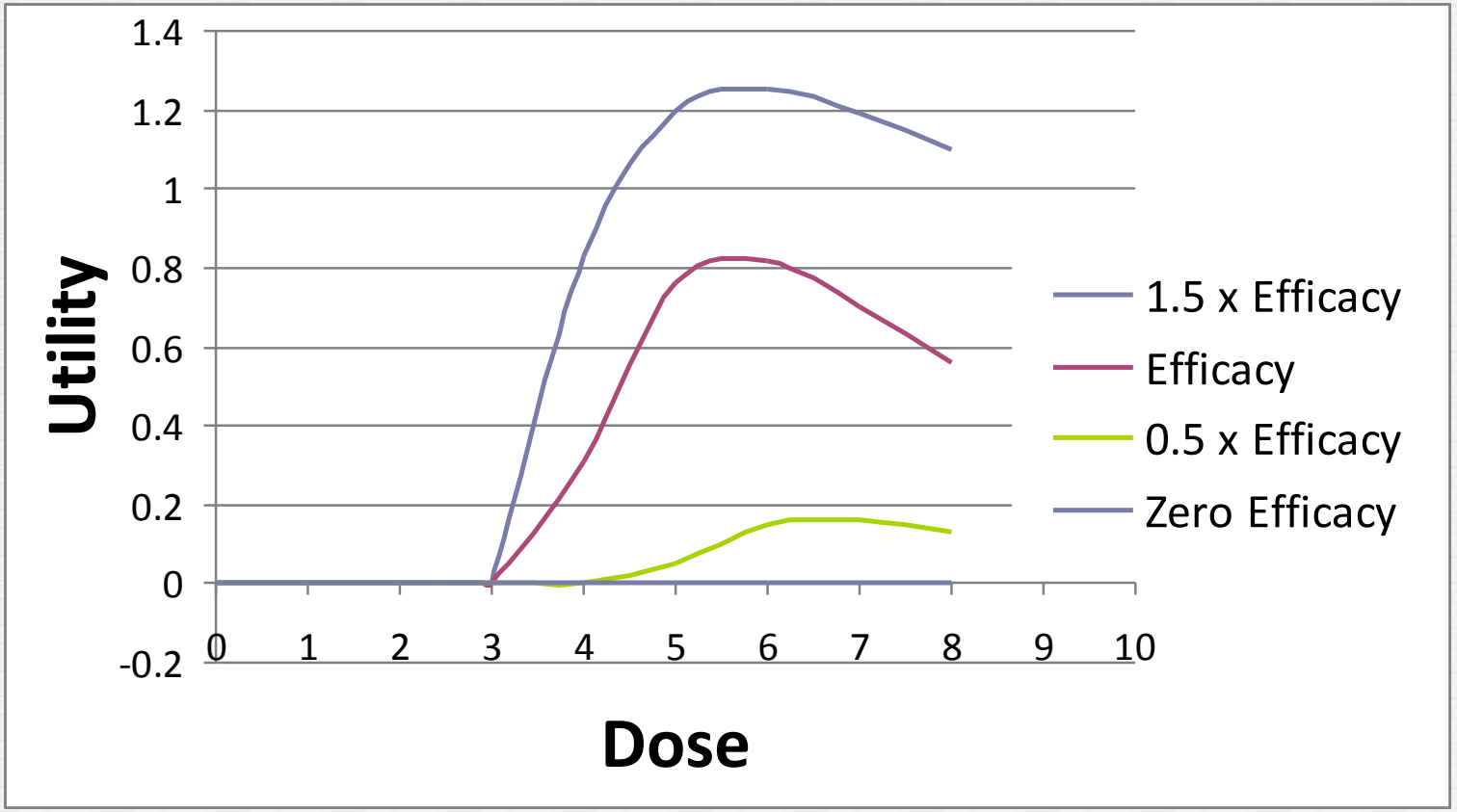
Target Dose Selection Method

Mean	0.90
Median	0.92
Std Dev	0.14

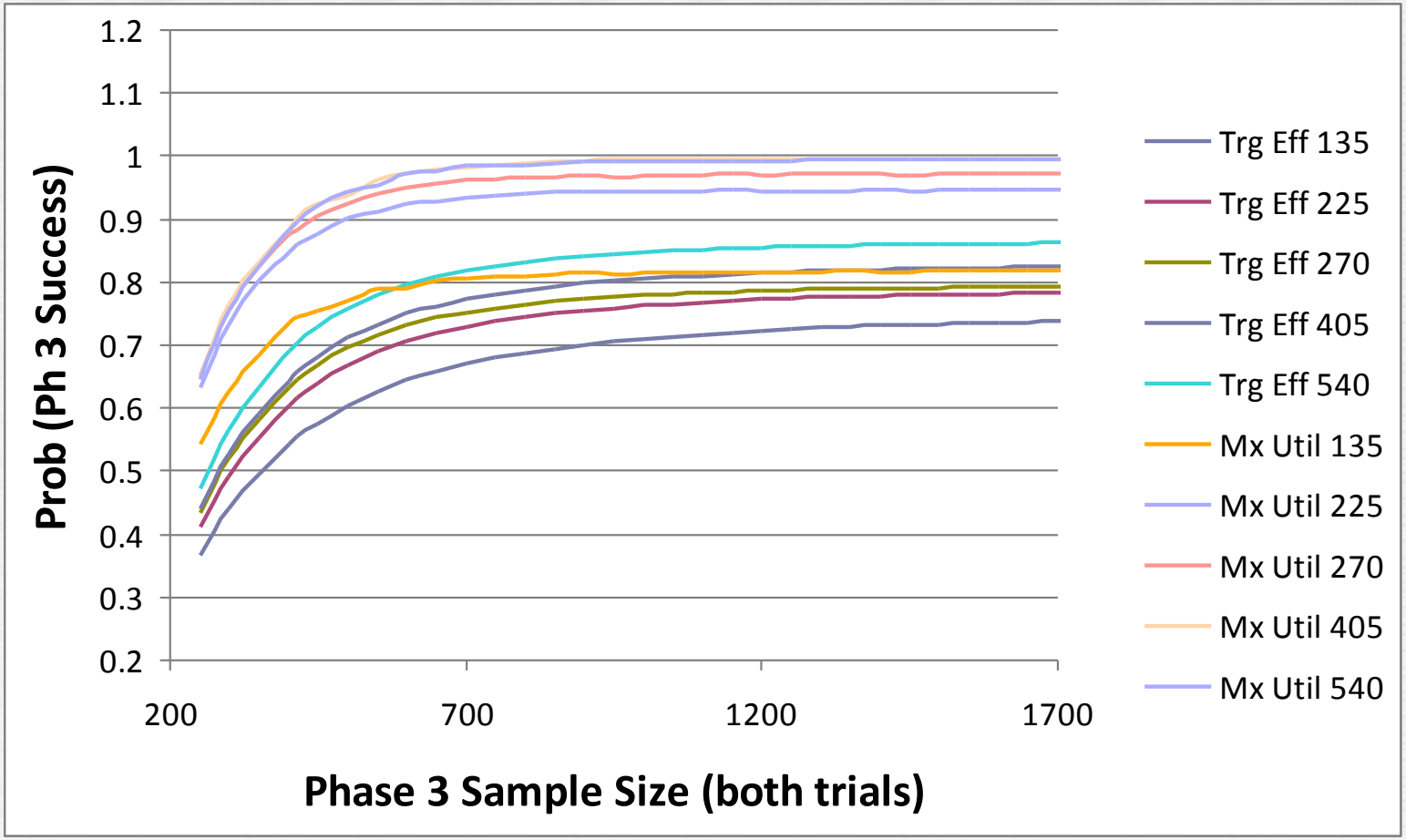
Accounting for downside risk

- Maximizing E(NPV) does not model risk. If a utility function is elicited for NPV the availability of distribution of NPV enables calculation of utilities for different Ph2 and Ph3 sample sizes.
- Assessing utility function can be difficult. A satisficing criterion of maximizing the probability of meeting or exceeding a specified target NPV can reflect risk.
- If the target is $B 0.8, Ph2 SS= 540 (pr = 0.86) is better than the ENPV maximizing SS of 270 (pr = 0.79).
- Can also use Target and linear loss functions on either side (Birge and Louveaux)

Utility function



PoS for Ph 2 and Ph 3 Sample Sizes (no ICH guidance minimum)



Base Case

Ph 2 Sample Size = 270

Ph 3 Dose is selected based on closeness to Target Dose

Dose Response Curve	Ph 2 Power	Prob. of going to Phase 3	Prob. Ph3 Success	Total Dev Time (Yrs)	Expected NPV ($B)
1.5 x Efficacy	1.00	0.99	0.97	7.1	3.15
Efficacy	0.97	0.80	0.80	7.1	1.95
0.5 x Efficacy	0.55	0.16	0.16	7.1	0.071
Zero Efficacy	0.036	0.002	0.000001	7.1	-0.0017