AN ADAPTIVE DOSE FINDING DESIGN (DOSEFIND) USING A NONLINEAR DOSE RESPONSE MODEL

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Thanks to

Dr. R. K. Elswick
Dr. Chris Gennings
Dr. Ramesh Ramakrishnan

For support and guidance

Objectives

- Motivation for the DOSEFIND
- How the DOSEFIND Works
- Simulation Plan/Results of DOSEFIND
- Conclusions

DOSEFIND Motivation

- Evaluate a pharmacodynamic (PD) marker that is indicator of efficacy in addition to safety considerations
- Describe a sigmoidal dose response curve using an adaptive approach with a non-linear methodology
- Quickly evaluate and eliminate dose levels below the no effect level (NOEL)
- Potential to provide significant time savings in later Phases of clinical trials development

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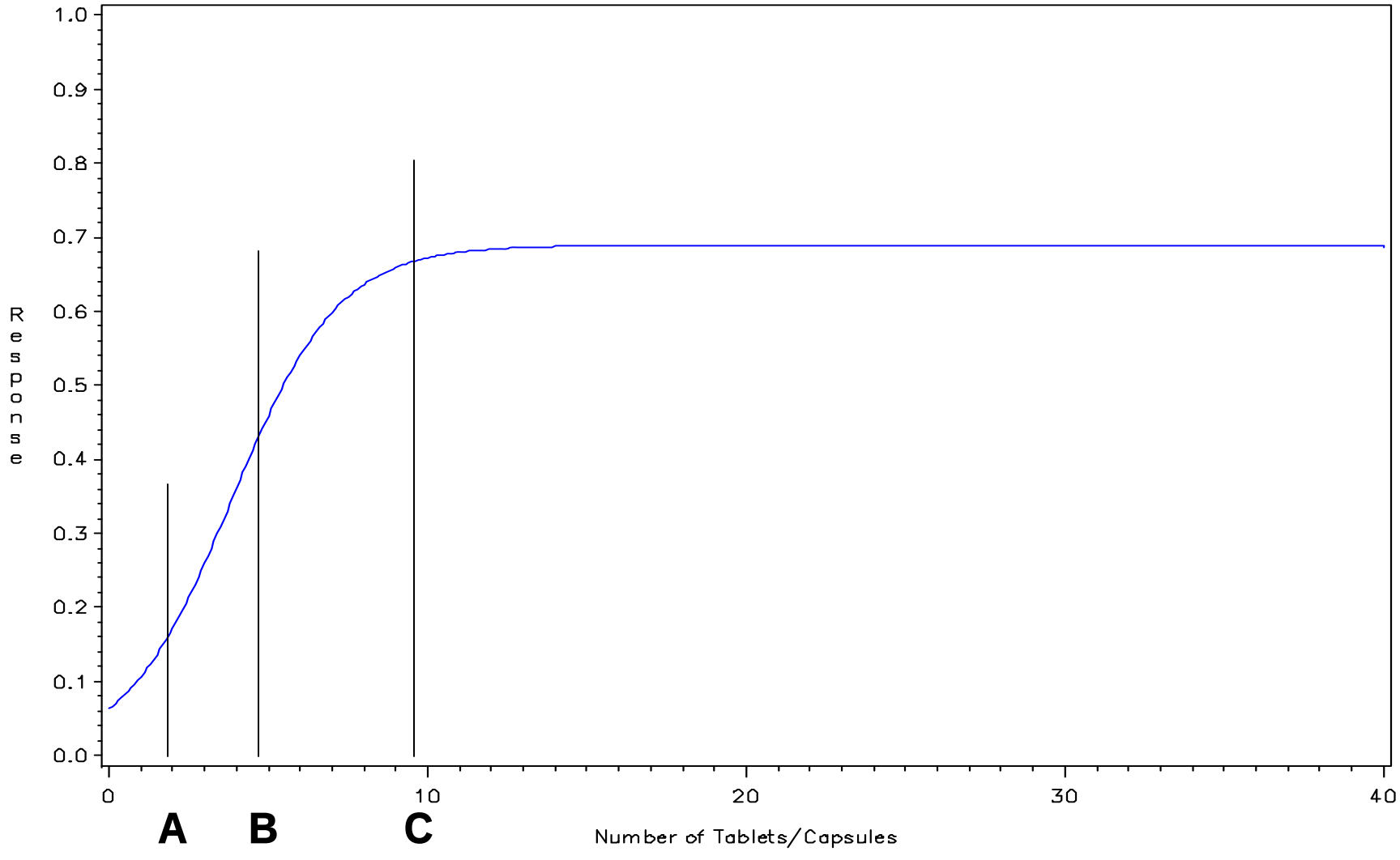
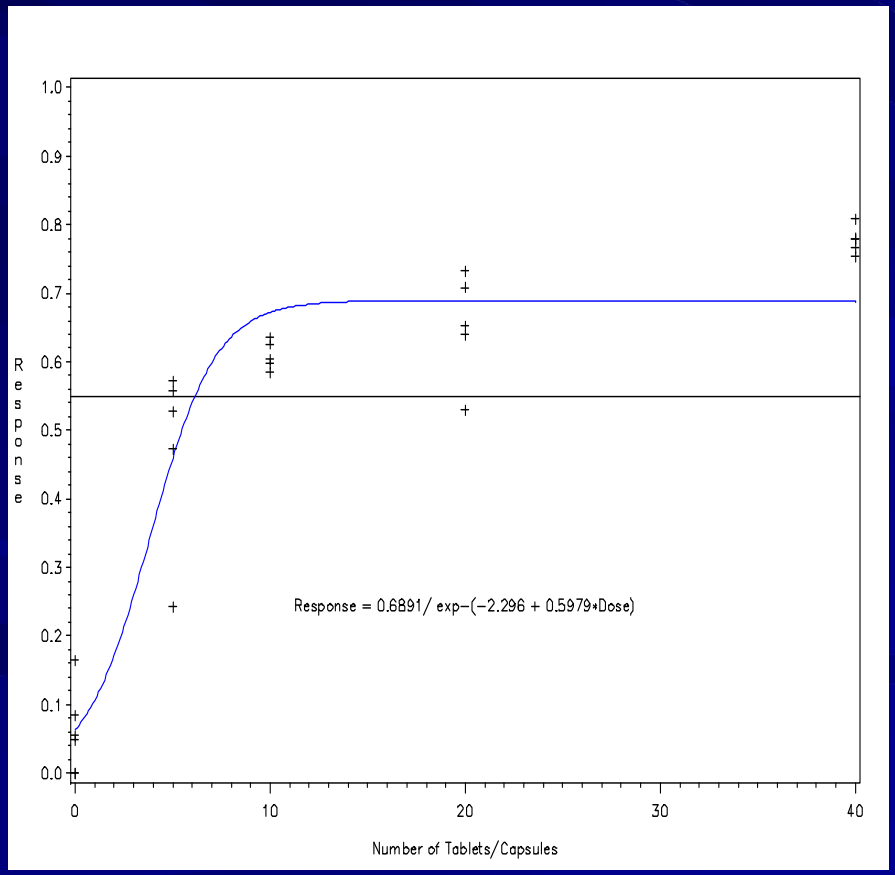
How the DOSEFIND Works



How the DOSEFIND Works
An Illustration

Clinical Trials Example Data



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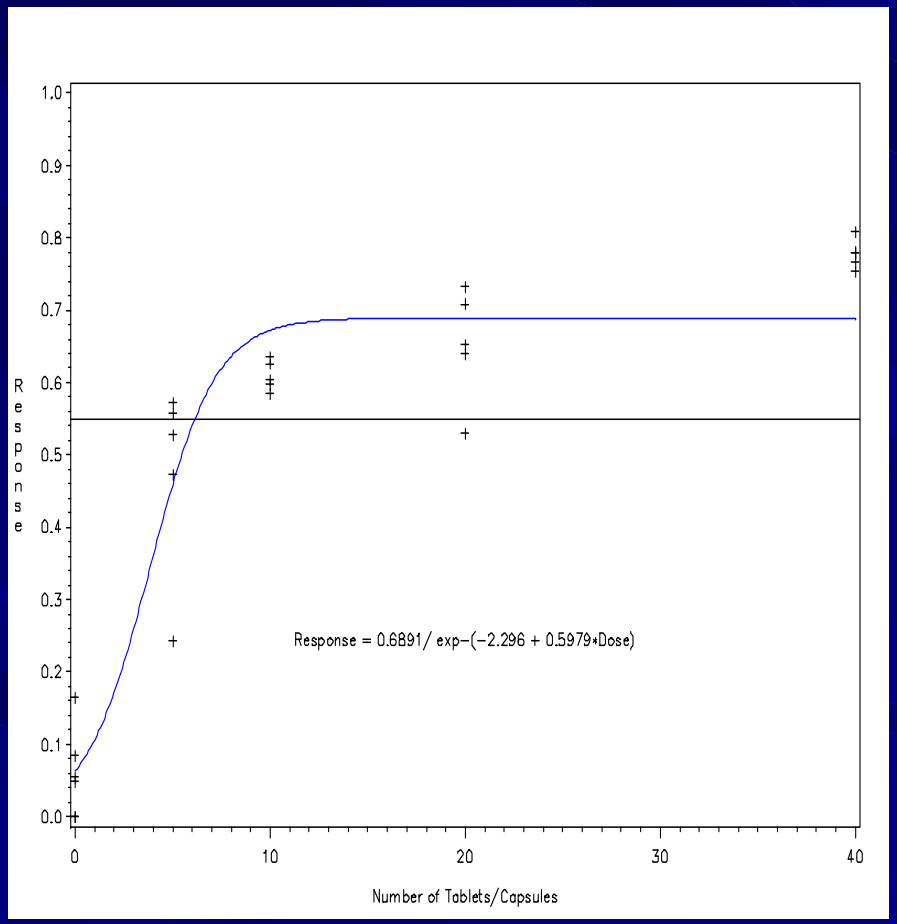
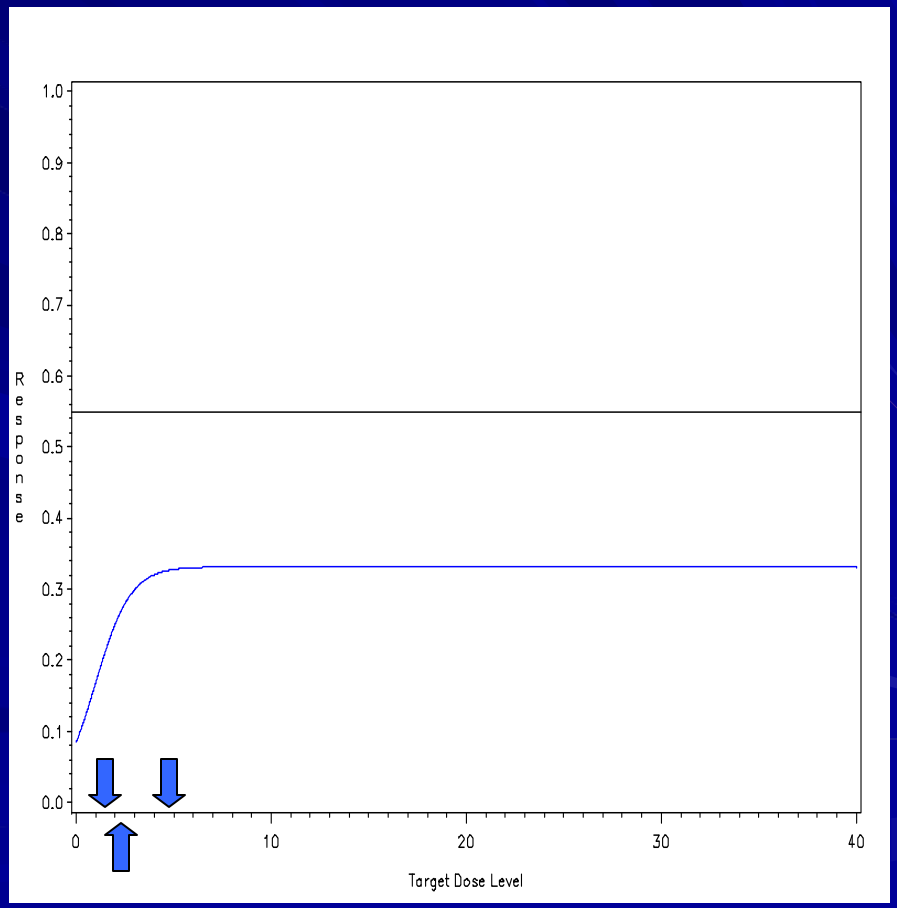


Illustration (1st Iteration)



How the DOSEFIND Works
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Clinical Trials Example Data

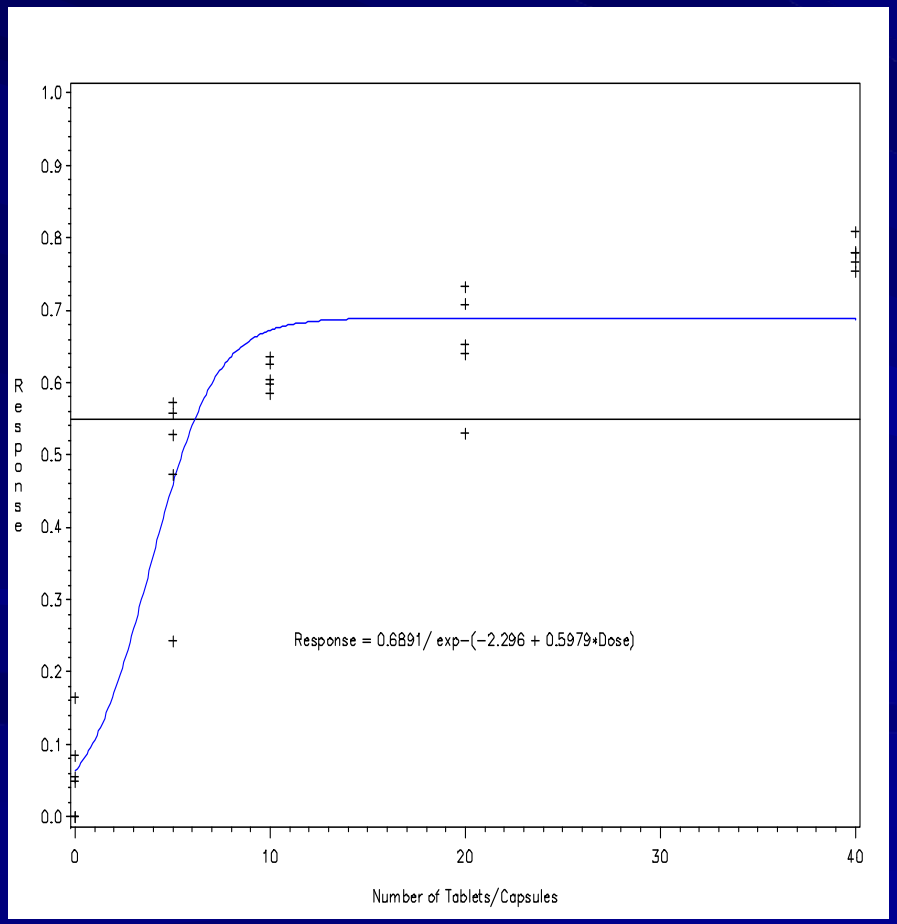
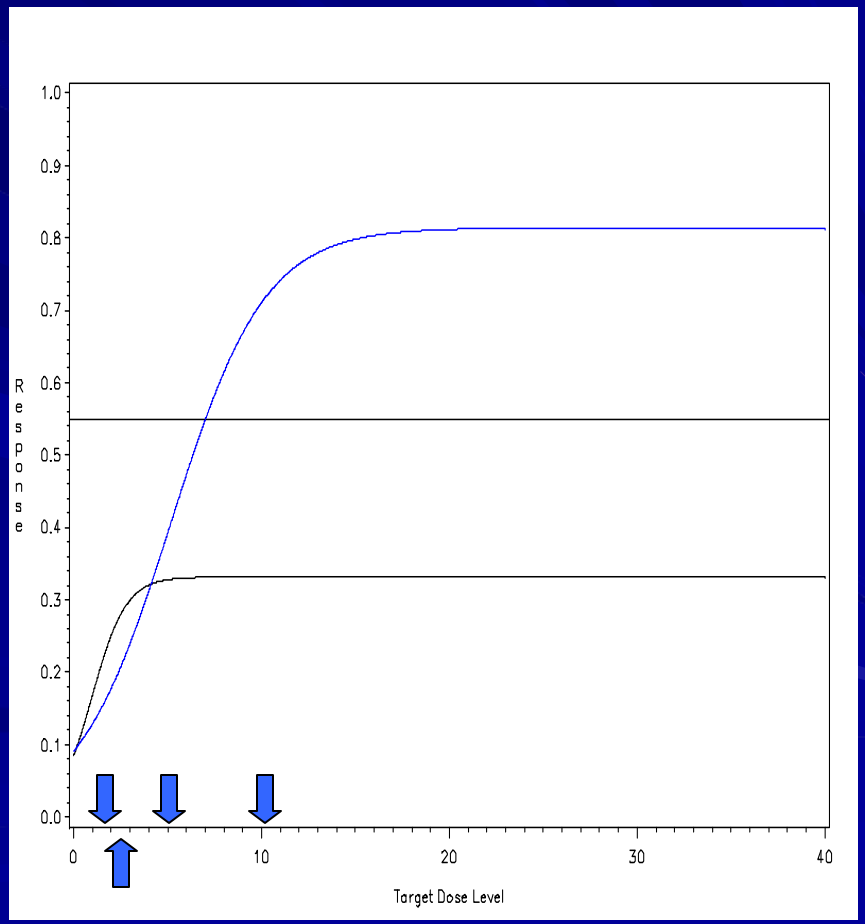


Illustration (2nd Iteration)



How the DOSEFIND Works
An Illustration

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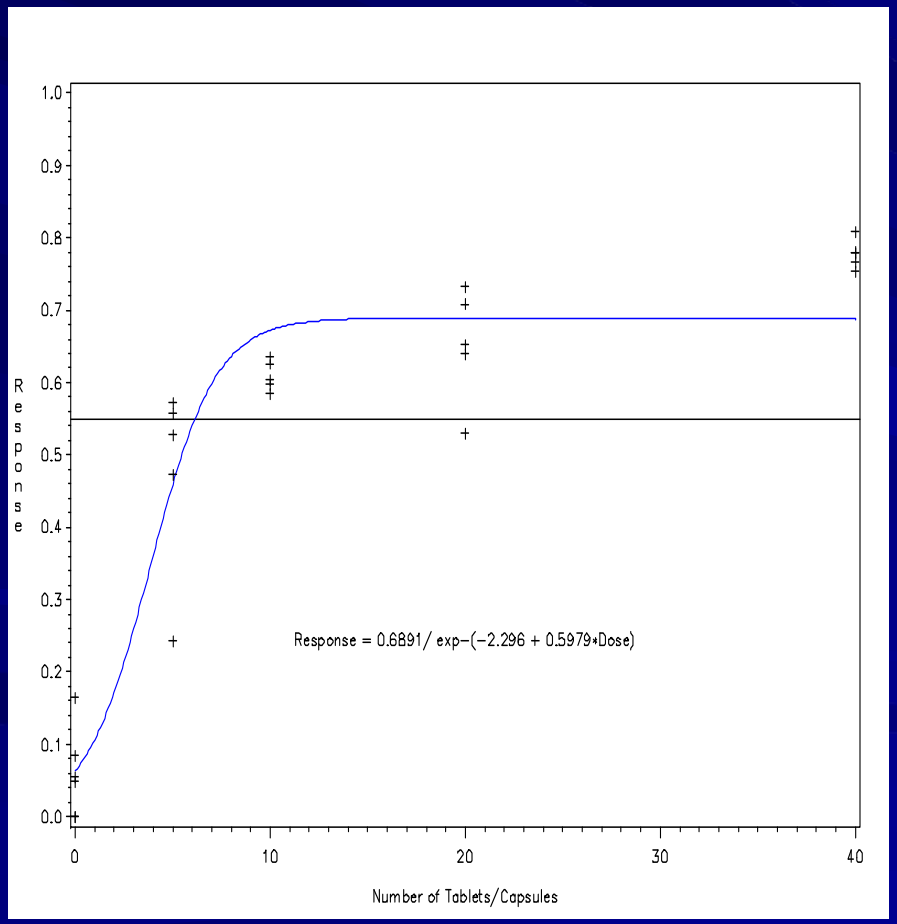

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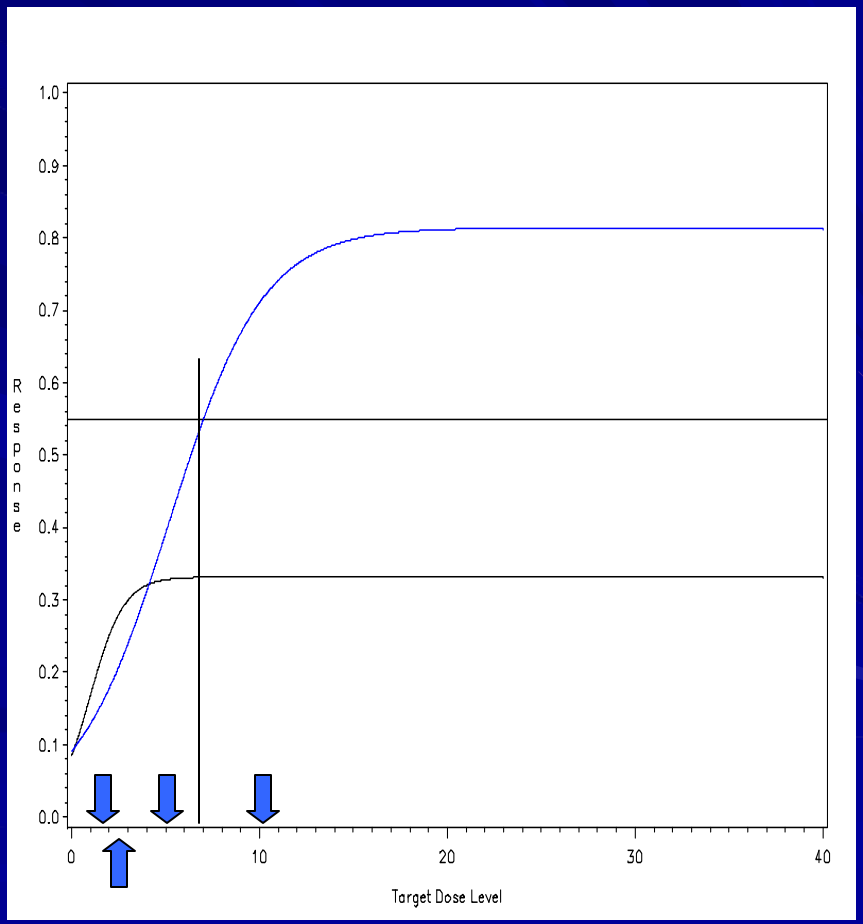

How the DOSEFIND Works An Illustration

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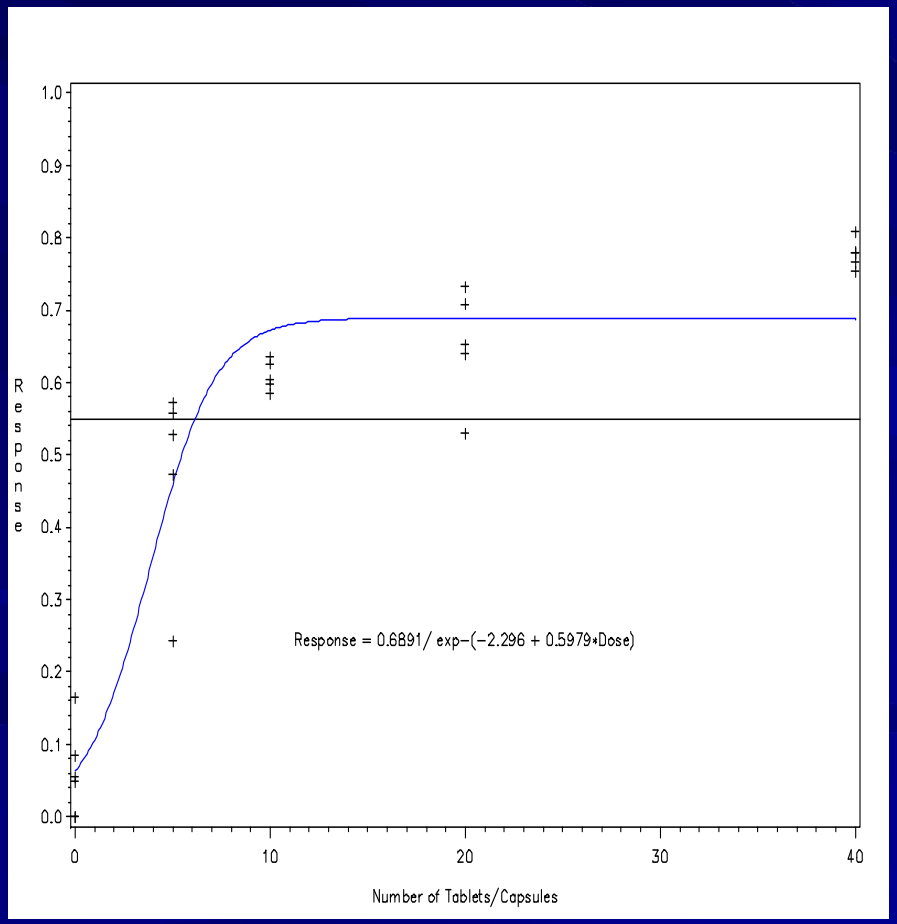
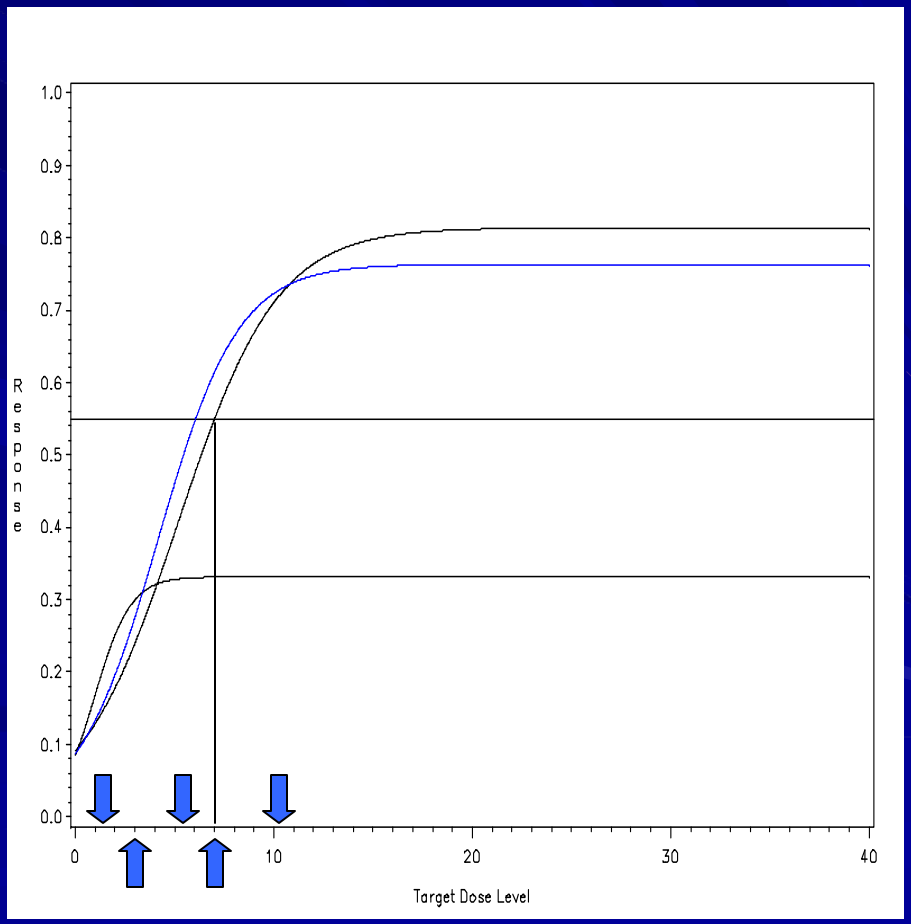


Illustration (3rd Iteration)



How the DOSEFIND Works
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Clinical Trials Example Data

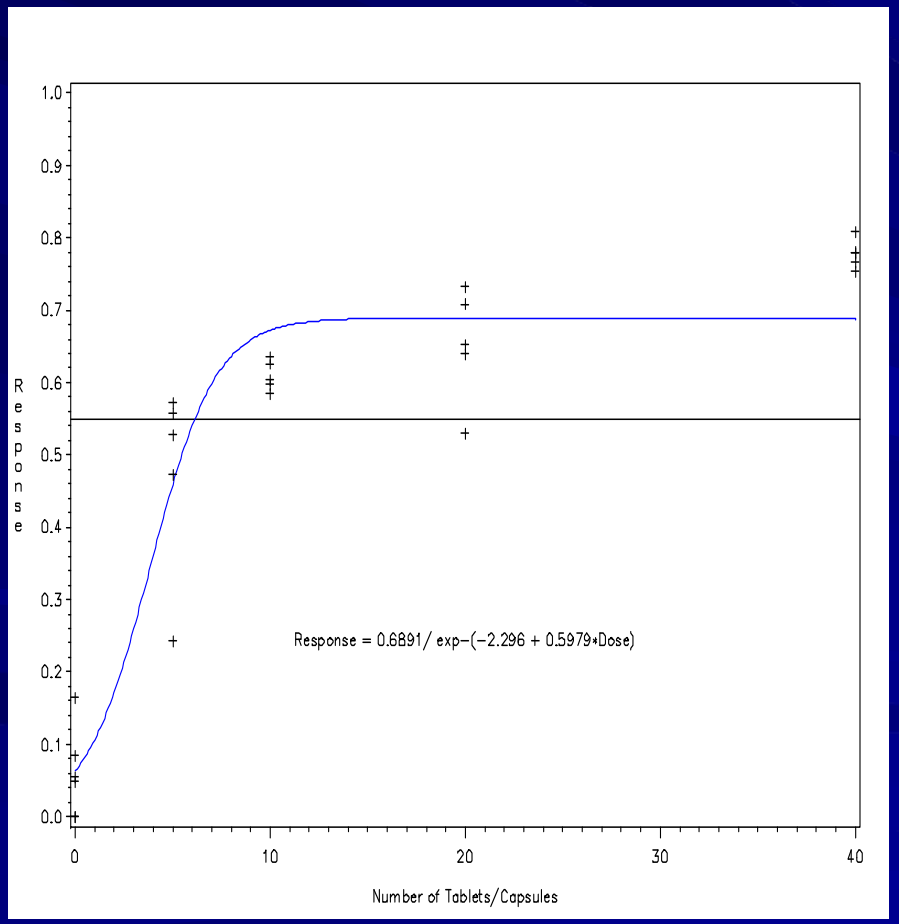
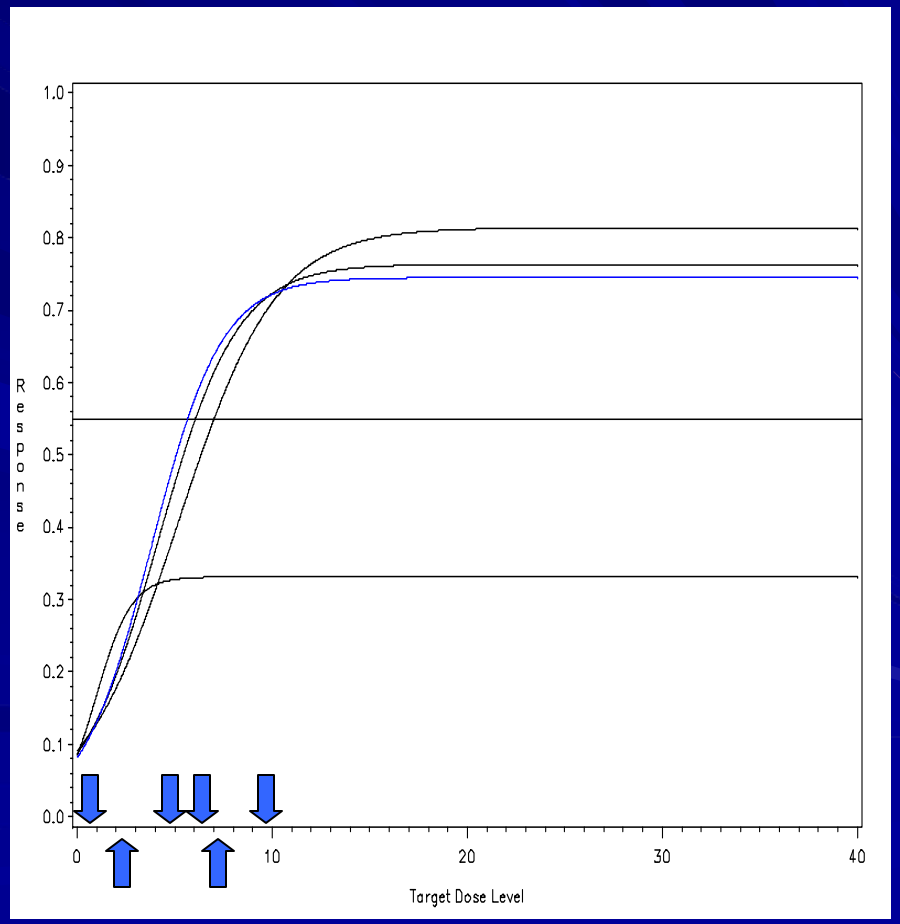


Illustration (4th Iteration)



How the DOSEFIND Works
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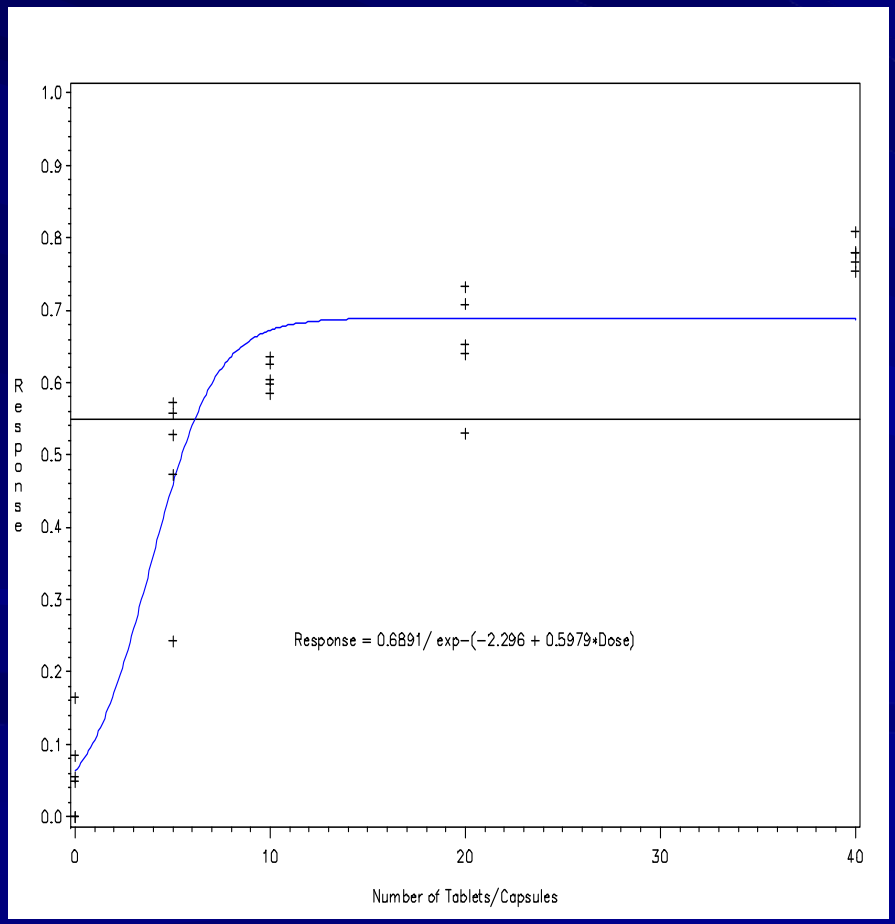
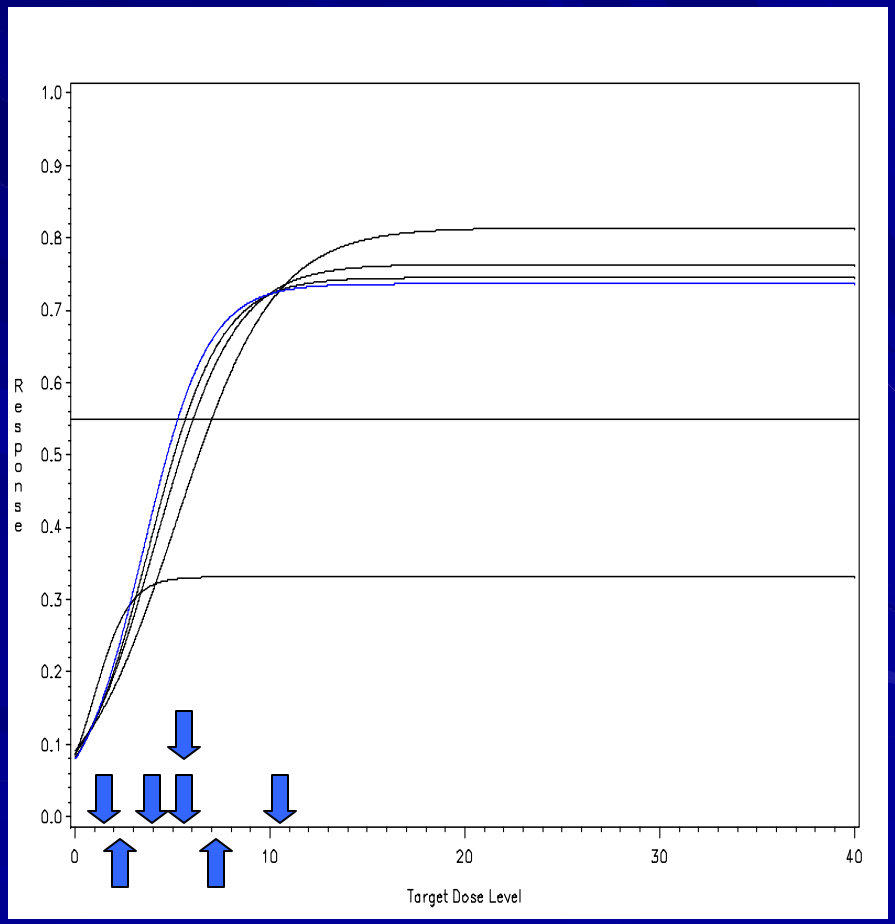


Illustration (5th Iteration)



How the DOSEFIND Works An Illustration

Clinical Trials Example Data

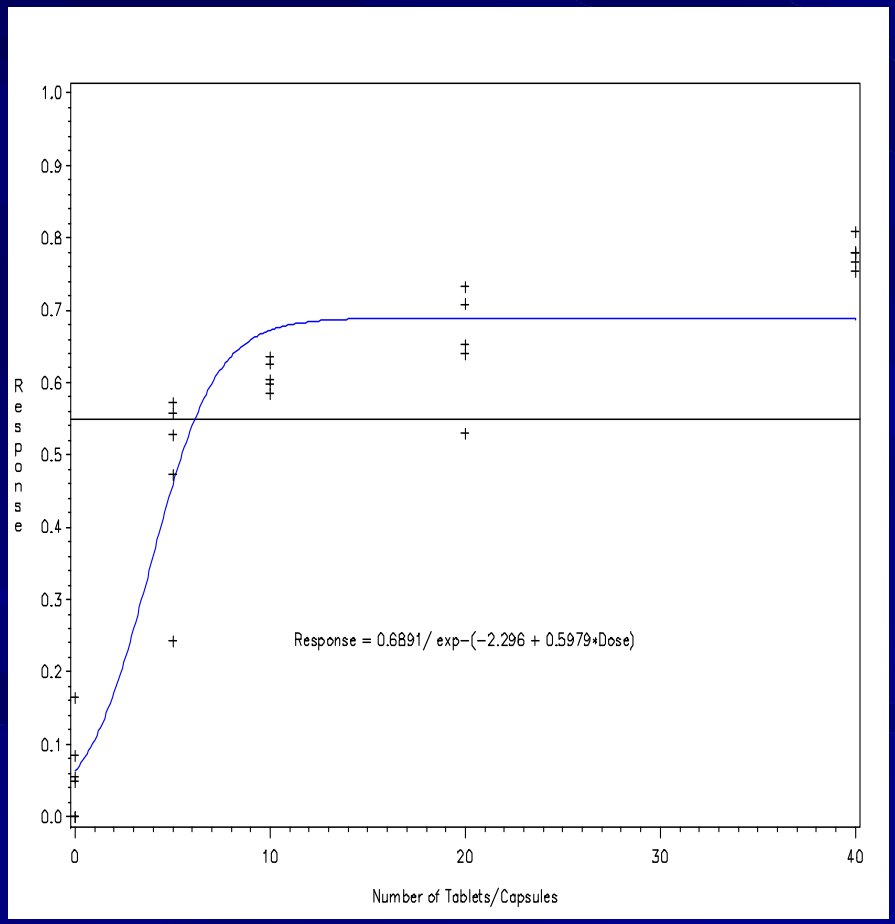
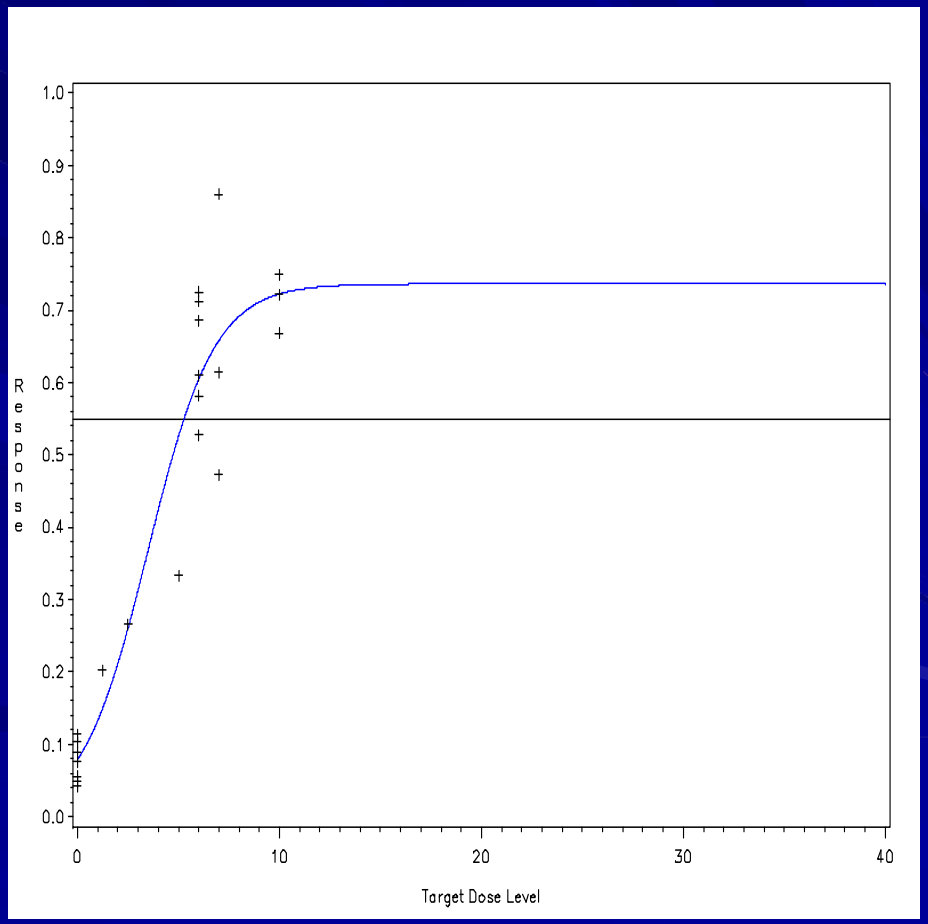


Illustration Final Curve



How the DOSEFIND Works An Illustration

- Example Trial n=20, DOSEFIND n=15
- Target T_D is 6.14 at a threshold response of 0.55
- DOSEFIND estimates T_D as 5 or 6 (5.27 ± 0.44)
- DOSEFIND puts all doses in the linear range

How the DOSEFIND Works

The general form of the non–linear model is:

$$\mu = \alpha + \gamma F\left(\mathbf{D}; \underset{\sim}{\mathbf{B}}\right)$$

where

D is the set of doses $\mathbf{D} = \left\{ d^{(1)}, \ldots, \quad d^{(k)} \right\}$ and
k is the number of dose steps

μ denotes the unknown effect

$\underset{\sim}{\mathbf{B}}$ denotes the vector of unknown parameters and

α is the minimum and

$\alpha+\gamma$ is the maximum unknown effect parameter

How the DOSEFIND Works

Illustrate DOSEFIND with the following 3 models:

Non-linear Logistic

$$\mu = \alpha + \frac{\gamma}{1 + e^{-(\beta_0 + \beta_1 \mathbf{D})}}$$

Michaelis-Menten

$$\mu = \alpha + \frac{\gamma * \mathbf{D}}{\phi + \mathbf{D}}$$

Gompertz

$$\mu = \alpha + \gamma e^{-e(-(\beta_0 + \beta_1 \mathbf{D}))}$$

How the DOSEFIND Works

Calculation of (T_D) for each model:

Logistic: $$T_D = \frac{\log\left(\mu_{T_D} / \left(\gamma - \mu_{T_D}\right)\right) - \beta_0}{\beta_1}$$

Gompertz: $$T_D = \frac{-\log\left(\log\left(\gamma / \mu_{T_D}\right)\right) - \beta_0}{\beta_1}$$

Michaelis-Menten: $$T_D = \phi\left(\frac{\mu_{T_D} - \alpha}{\gamma - \mu_{T_D} + \alpha}\right)$$

Objectives

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Simulation Plan

- The four different assignment schemas are:

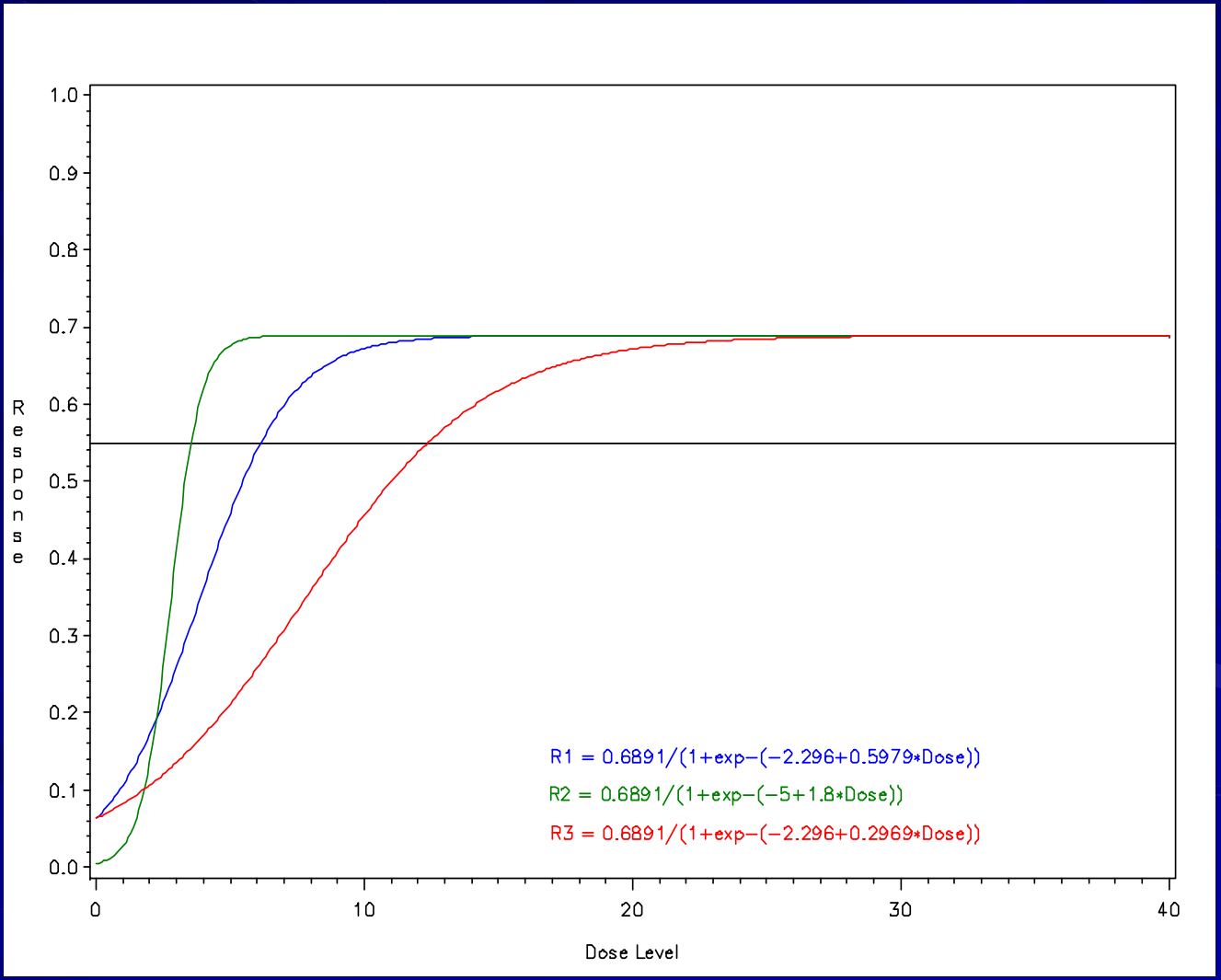
Initial 3 Dose Levels			All Subsequent Dose levels		
	Active	Placebo		Active	Placebo
(1, 1)	1	1	(1, 1)	1	1
(3, 1)	3	1	(1, 1)	1	1
(1, 1)	1	1	(3, 1)	3	1
(3, 1)	3	1	(3, 1)	3	1

Simulation Plan

- The shape of the logistic model is modified by choosing different slopes and intercepts:
  - $\beta_0 = -2.3$ and $\beta_1 = 0.60$, Base Model (SIM 1)
  - $\beta_0 = -5$ and $\beta_1 = 1.8$, Steep slope (SIM 2)
  - $\beta_0 = -2.3$ and $\beta_1 = 0.30$, Shallow slope (SIM 3)

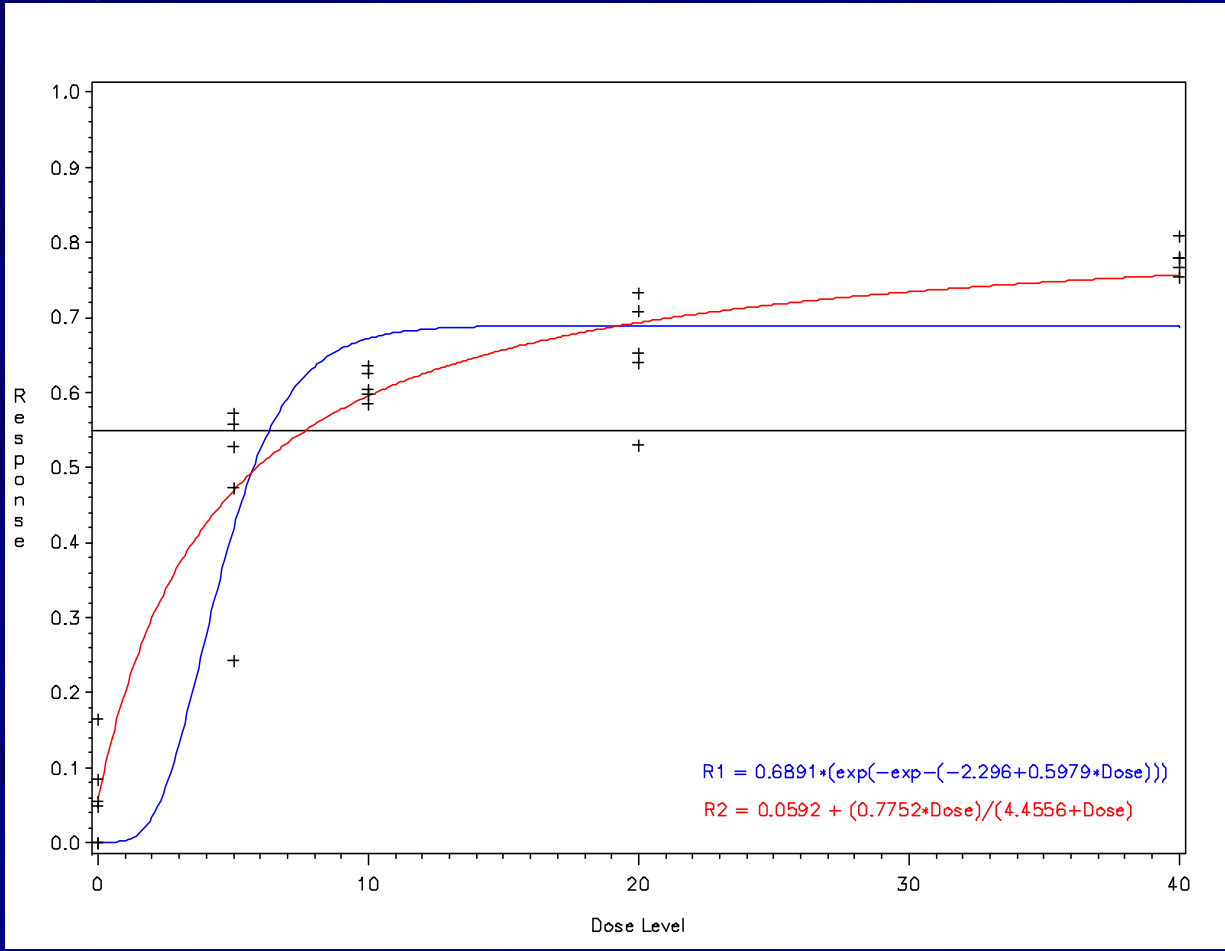
Simulation Plan

Non-Linear Logistic Base Model (R1), Steep Slope (R2) and Shallow Slope (R3)



Simulation Plan

Gompertz (R1) and Michaelis-Menten (R2) Non-Linear Functions

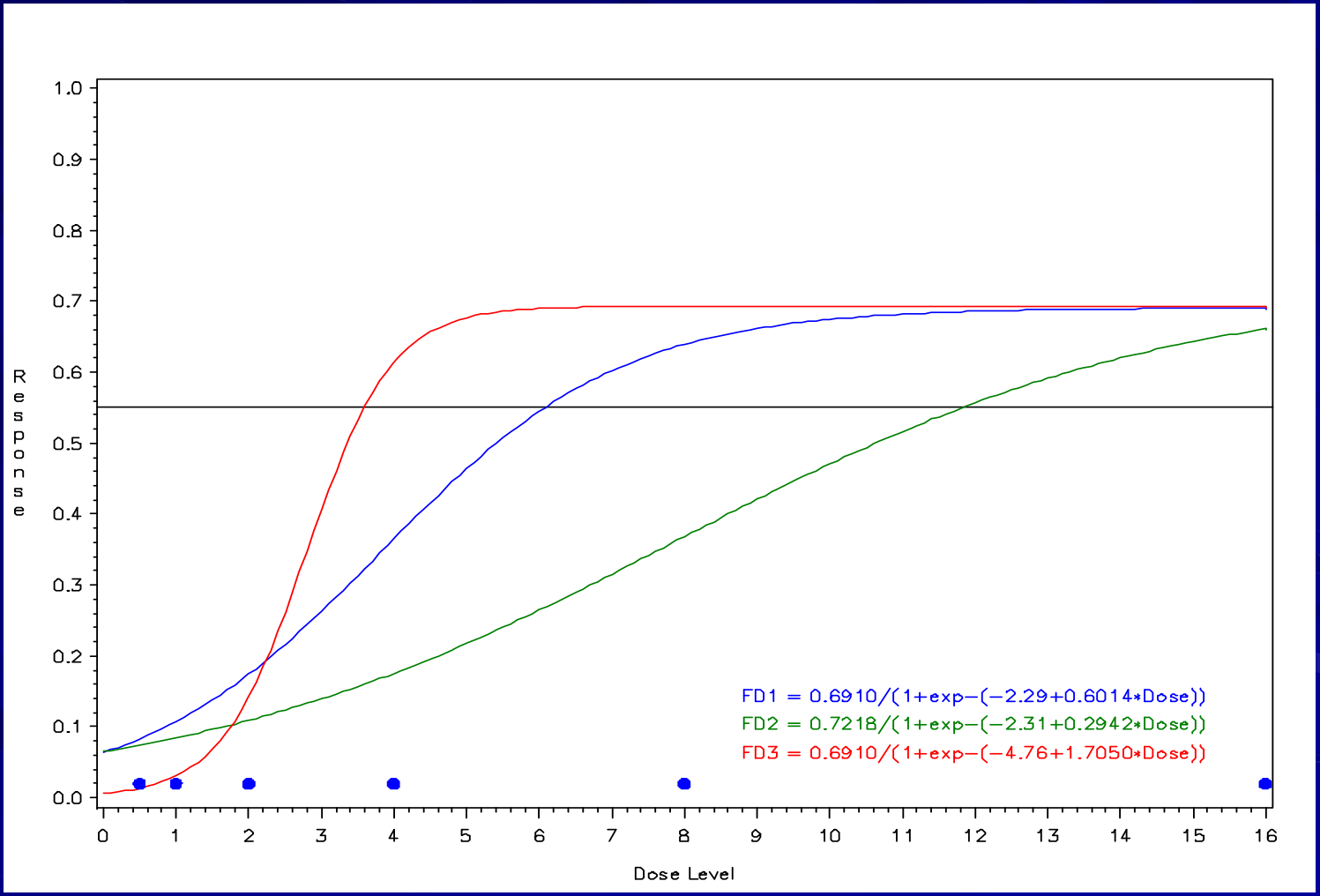


Simulation Plan

Expected Values of T_D for the Target Threshold Effect

	Dose Levels				
Target Threshold Effect	SIM 1 Non-Linear Logistic	SIM 2 Steep β_1	SIM 3 Shallow β_1	SIM 4 Gompertz	SIM 5 Michaelis-Menten
0.55	6.14	3.54	12.36	6.83	7.69

Fixed Dose Simulations



DOSEFIND Results

Results from SIM 1 (10 simulations of size n=100 each) for four sampling scenarios

Desired Response: 0.55 and Desired Target Dose: 6.14				
Run*	Mean Parameter Estimates and Standard Error			
	T_D	D_N	½-width 95% CI	ARE
1-1, 1-1	6.18 (0.060)	9.00 (0.306)	0.639 (0.017)	50%
3-1, 1-1	6.09 (0.047)	7.98 (0.201)	0.583 (0.004)	47%
1-1, 3-1	6.21 (0.035)	6.99 (0.108)	0.466 (0.017)	37%
3-1, 3-1	6.15 (0.036)	6.40 (0.082)	0.435 (0.015)	35%

ARE: Asymptotic Relative Efficiency WRT a “fixed dose” design
Fixed Dose “Base” model $\sigma^2=0.596$

DOSEFIND Results

Results from SIM 2 (10 simulations of size n=100 each) for four sampling scenarios

Desired Response: 0.55 and Desired Target Dose: 3.54				
Run*	Mean Parameter Estimates and Standard Error			
	T_D	D_N	½-width 95% CI	ARE
1-1, 1-1	3.72 (0.052)	5.19 (0.031)	0.192 (0.006)	35%
3-1, 1-1	3.67 (0.023)	5.02 (0.014)	0.150 (0.004)	29%
1-1, 3-1	3.69 (0.038)	5.09 (0.040)	0.126 (0.006)	24%
3-1, 3-1	3.71 (0.037)	5.01 (0.008)	0.089 (0.003)	18%

Fixed Dose "Steep Slope" model $\sigma^2=0.236$

DOSEFIND Results

Results from SIM 3 (10 simulations of size n=100 each) for four sampling scenarios

Desired Response: 0.55 and Desired Target Dose: 12.36				
Run*	Mean Parameter Estimates and Standard Error			
	T_D	D_N	½-width 95% CI	ARE
1-1,1-1	12.34 (0.0878)	16.87 (0.4558)	0.847 (0.013)	25%
3-1,1-1	12.23 (0.1000)	16.09 (0.4480)	0.833 (0.007)	25%
1-1,3-1	12.38 (0.0644)	11.90 (0.4026)	0.728 (0.019)	22%
3-1,3-1	12.31 (0.0506)	11.51 (0.4277)	0.704 (0.017)	21%

Fixed Dose "Shallow Slope" model $\sigma^2=1.639$

DOSEFIND Results

Results from simulation (10 simulations of size n=100 each) for the Gompertz (SIM 4), the Michaelis-Menten Nonlinear (SIM 5) and the Non-Linear Logistic with Safety Adjustment (SIM 6) Models

Desired Response: 0.55 and Desired Target Dose: 6.83, 7.69 and 6.14			
Run*	Mean Parameter Estimates and Standard Error		
	T_D	½-width 95% CI	σ^2
Gompertz	6.83 (0.031)	0.678 (0.019)	0.33 (0.009)
Michaelis-Menten	7.44 (0.058)	0.738 (0.02)	0.36 (0.010)
Non-linear Logistic + Safety	6.22 (0.055)	0.473 (0.02)	0.22 (0.001)

Sampling Schema (1-1,3-1)

DOSEFIND Results

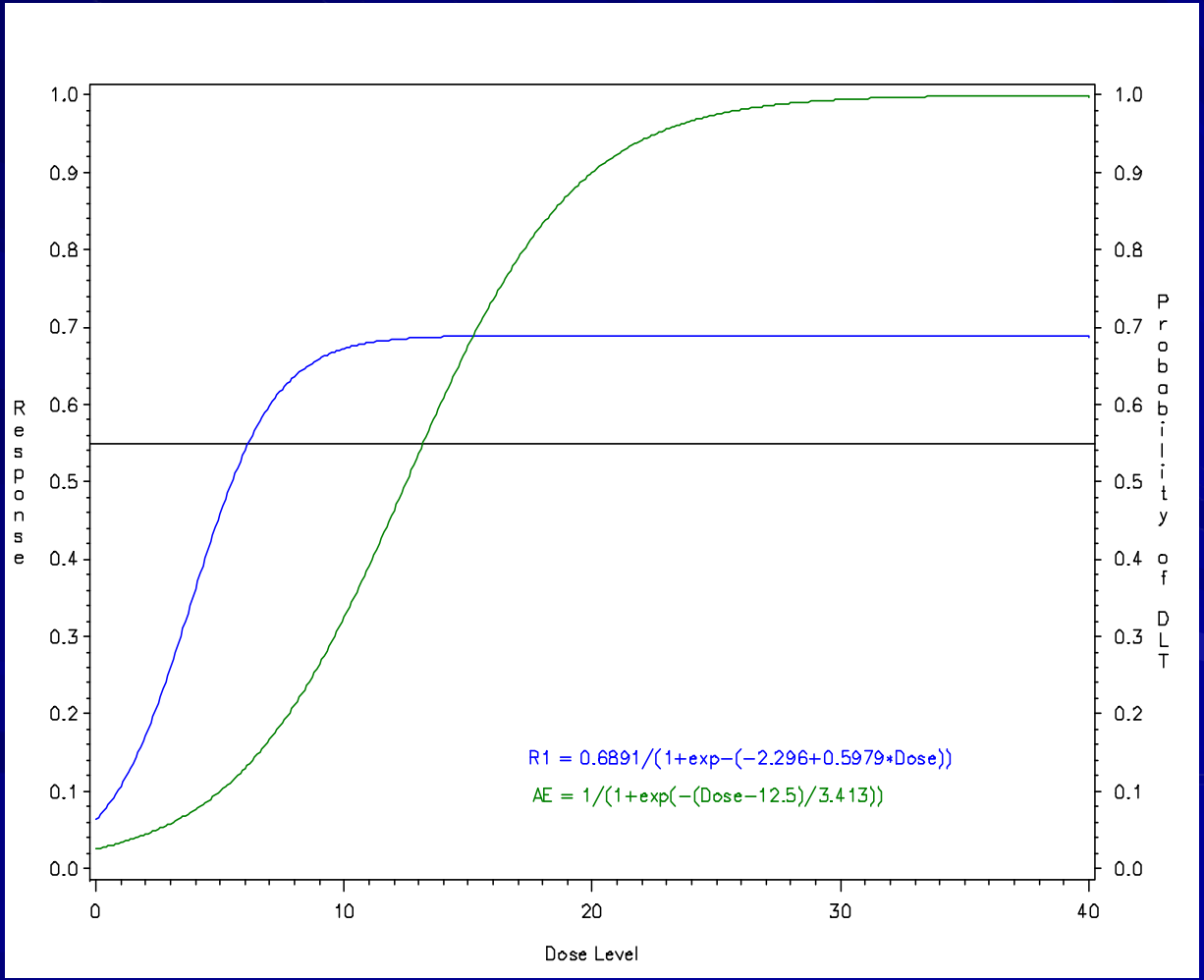
Simulations that stopped prior to convergence of the confidence interval

Stopping Rates for Each Simulation					
Run	SIM 1 Non-Linear Logistic	SIM 2 Steep β_1	SIM 3 Shallow β_1	SIM 4 Gompertz	SIM 5 Michaelis-Menten
1-1, 1-1	1.6%	0%	24%	-	-
3-1, 1-1	0.4%	0%	24%	-	-
1-1, 3-1	0%	0%	1.5%	4.5%	3.3%
3-1, 3-1	0%	0%	1.4%	-	-

* Percentage of runs that stopped due to an adverse event

Simulation including Probability of a DLT

Non-Linear Logistic (R1) with Adverse Event (AE) Probability Curve



DOSEFIND Results

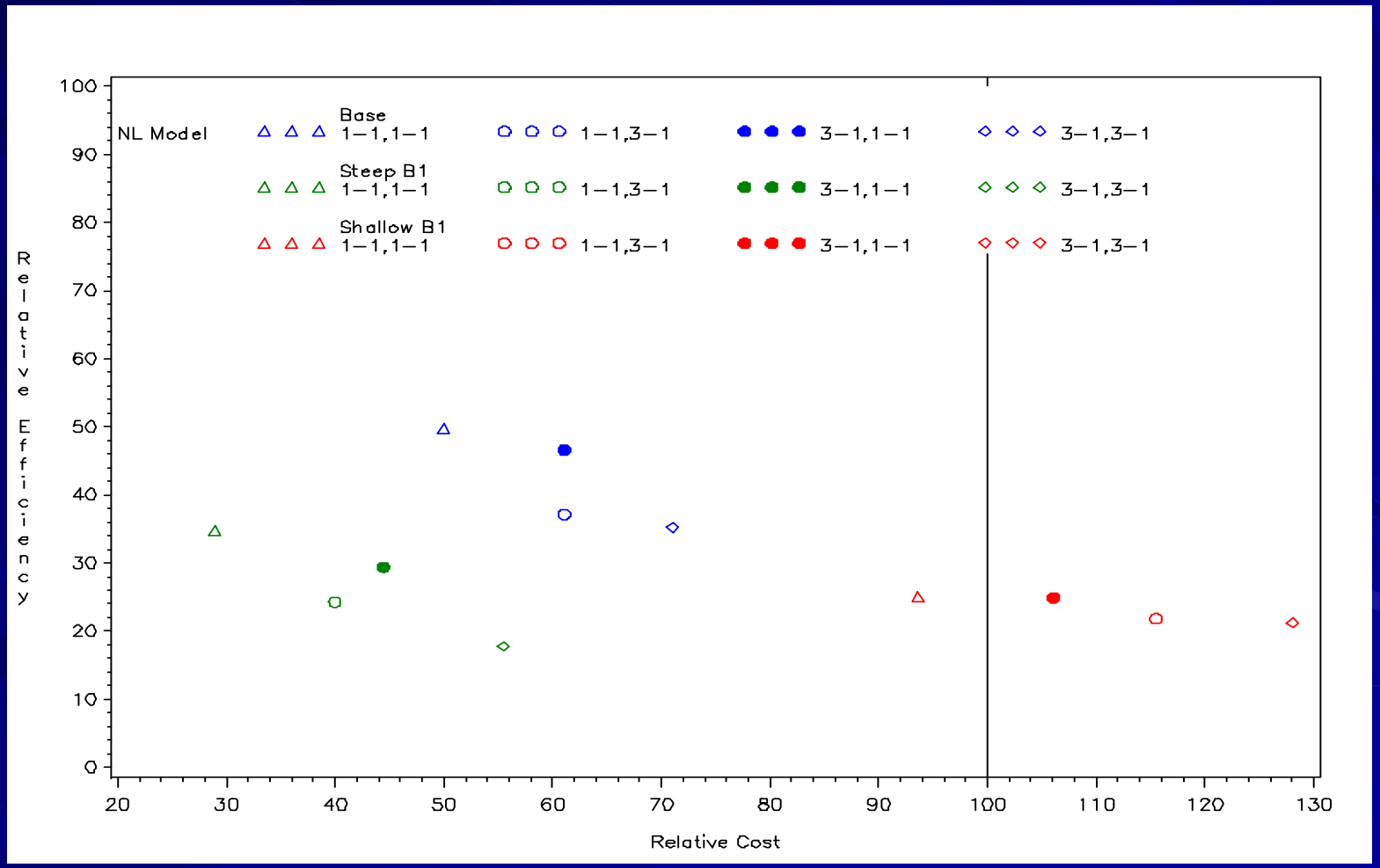
Simulations that stopped prior to convergence of the confidence interval

Stopping Rates for Each Simulation						
Run	SIM 1 Non-Linear Logistic	SIM 2 Steep β_1	SIM 3 Shallow β_1	SIM 4 Gompertz	SIM 5 Michaelis-Menten	SIM 6 Non-Linear Logistic + Safety
1-1, 1-1	1.6%	0%	24%	-	-	-
3-1, 1-1	0.4%	0%	24%	-	-	-
1-1, 3-1	0%	0%	1.5%	4.5%	3.3%	19.8%*
3-1, 3-1	0%	0%	1.4%	-	-	-

* Percentage of runs that stopped due to an adverse event

DOSEFIND Results

Comparison of Relative Efficiency versus Relative Cost, for Base (SIM 1), Steep (SIM 2) and Shallow (SIM 3) Nonlinear Logistic Models



Conclusions

- Developed an Adaptive Method that:
  - produces a dose response curve profile of a desired PD parameter
  - the choice of the functional form is not sensitive to the estimation of the T_D
  - is more efficient as measured by ARE to a “fixed dose” design
  - is more cost effective as measured by sample size to a “fixed dose” design

Conclusions

- Uses general non-linear 3 and 4 parameter models
- General structure for variance
- Use early trials in humans to assess efficacy as well as safety

Background: Modified CRM Design

- Piantadosi et.al. 1997
  - Model: $\Pr[toxicity] = \frac{1}{1 + e^{-\beta(d - d_{50})}}$
  - Logistic regression
  - Not using fixed set of dose levels
  - Assigns patients based on new d30
  - Does not estimate the variance of the target dose
  - Based on observance of toxicity

How the DOSEFIND Works

The variance of Y is assumed to be a function of the mean, that is,

$$\mathrm{Var}(Y) = \tau V(\mu)$$

Under the premise that the observed variance is larger in the "linear" portion of the dose response curve for responses between zero and one, $V(\mu)$ is assumed to follow $\mu(1-\mu)$

How the DOSEFIND Works

Let $\mathbf{G}_i = \alpha + \gamma \mathbf{F}\left(d^{(i)}, \underset{\sim}{\mathbf{B}}\right)$ and let $\mathbf{H}$ be the partial derivatives from the (T_D) equations, then $\boldsymbol{\Sigma}$ and $\mathrm{Var}(\hat{T}_D) = \mathbf{H}\boldsymbol{\Sigma}\mathbf{H}'$ are derived using the quasi-likelihood approach found in Seber and Wild (1989)

How the DOSEFIND Works

- The estimate of the target dose (T_D) for the general nonlinear form is:

$$T_D = \frac{F^{-1}\left(\left(\mu_{T_D} - \alpha\right)/\gamma\right) - \beta_0}{\beta_1}$$

How the DOSEFIND Works An Illustration

Illustration Results for the DOSEFIND Method

Steps	β_0	β_1	γ	Actual Dose	Target Dose	Variance	½ 95% CI
1	-1.0698	1.1054	0.33145	-	10.0	-	-
2	-2.07356	0.40014	0.81388	7.0176	7.0	0.7612	1.800
3	-2.05163	0.49431	0.76334	6.0664	6.0	0.5695	1.254
4	-2.10020	0.55409	0.74503	5.6615	6.0	0.2968	0.633
5	-2.1183	0.60724	0.73635	5.2707	5.0	0.2121	0.444

DOSEFIND Results

Results from SIM 7 (10 simulations of size n=100 each) for fixed dose levels

Desired Response: 0.55 and Desired Target Dose: 6.14, 3.54 and 12.36			
Run	Mean Parameter Estimates and Standard Error		
	T_D	½-width 95% CI	σ^2
Logistic	6.21 (0.0319)	1.212 (0.0108)	0.596 (0.0053)
Steep β1	3.62 (0.0101)	0.481 (0.0035)	0.236 (0.0017)
Shallow β1	12.62 (0.0588)	3.335 (0.9366)	1.639 (0.4603)

DOSEFIND Results

Comparison of Bias-Squared versus Mean Square Error for Nonlinear Logistic Models