Simulation for Designing and Analyzing Clinical Trials

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Stephan Ogenstad[1], Peter Westfall[3] Kuenhi Tsai[2]

[1]Statogen Consulting, NC
[2]Vertex Pharmaceuticals Incorporated, MA
[3]Texas Tech University, TX

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Overview

- Is Drug Development A House of Cards?
- How Do We Plan the Work, and Work the Plan?
- The Clinical Trials Simulation System
- The Statistics of the System
- Running the Application
- Examples

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Is Drug Development A House of Cards?

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Is Drug Development A House of Cards?

The industry will needs to reduce the cost of drug development by over 40%.

Kenneth Kaitin, PhD
Director, Tufts Center
for Study of Drug Development,
Tufts University

Many Drugs Fail In Clinical Development! Why?

- Inappropriate choice of disease
- Incorrect selection of the drug dose and schedule
- Poor target validation or lack of biological activity
- Not wanting to announce the “bad news” now
- Framing the problem too narrowly to bring it inside the comfort zone
- Being attached to ‘sunk costs’
- Assuming no uncertainty in potential outcomes
- Conspiracy of optimism
- Not seriously involving the right people
- Making decisions alone

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FDA's Critical Path Initiative: Mission

A serious attempt to bring attention and focus to the need for targeted scientific efforts to modernize the techniques and methods used to evaluate the safety, efficacy and quality of medical products as they move from candidate selection and design to mass manufacture.

How Do We Plan the Work, and Work the Plan?

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The Fifth Discipline: The Art & Practice of the Learning Organization by Peter M. Senge

- Team learning
- Building shared vision
- Mental models
- Personal mastery
- Systems thinking

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Technology's Emerging Role in Clinical Trials

To make product development more predictable and efficient:

- Streamlining clinical trials (Clinical trial simulations, Adaptive methods, Modeling, Enrichment designs)
- Biomarkers (genomics, proteomics, metabolomics, safety, personalized medicine)
- Bioinformatics
- New imaging techniques
- Disease models
- But, translational sciences have been relatively slow to embrace new technologies

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Successfully Implementing Modeling and Simulation Strategies

- Using results to train teams and sites
- Clinical development process (from phase I to phase III registration trials)
- Interdisciplinary approach between clinical pharmacologists, pharmacokineticists, statisticians, project planners and key decision makers on a project team

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Clinical Drug Development as Rational Model-Based Scientific Discipline

While the far future of scientific drug development is difficult to predict, successful advancement and integration of clinical trial simulation lead to a daring prediction: in the not so distant future, most clinical trials will be virtual – only a few actual trials will be undertaken. These few human trials will be designed to inform simulation models and to confirm model prediction.

Carl Peck, MD*

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* "Simulation for Designing Clinical Trials"

Problems Amenable to Grid Computing

- When you have …
  - Replicates of Fundamental tasks
  - Fundamental tasks are time consuming, lots of replicates
- Then grid computing is ideal

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For Clinical Trials Simulation

- Fundamental task: Each data set generation, evaluation of “success” criteria
- Replications = Simulations
- Each task is time-consuming
  - Many variables
  - Many calculations: Principal components, nonlinear least squares fits
  - Sorts, transposes, reshapes on 1000’s of obs

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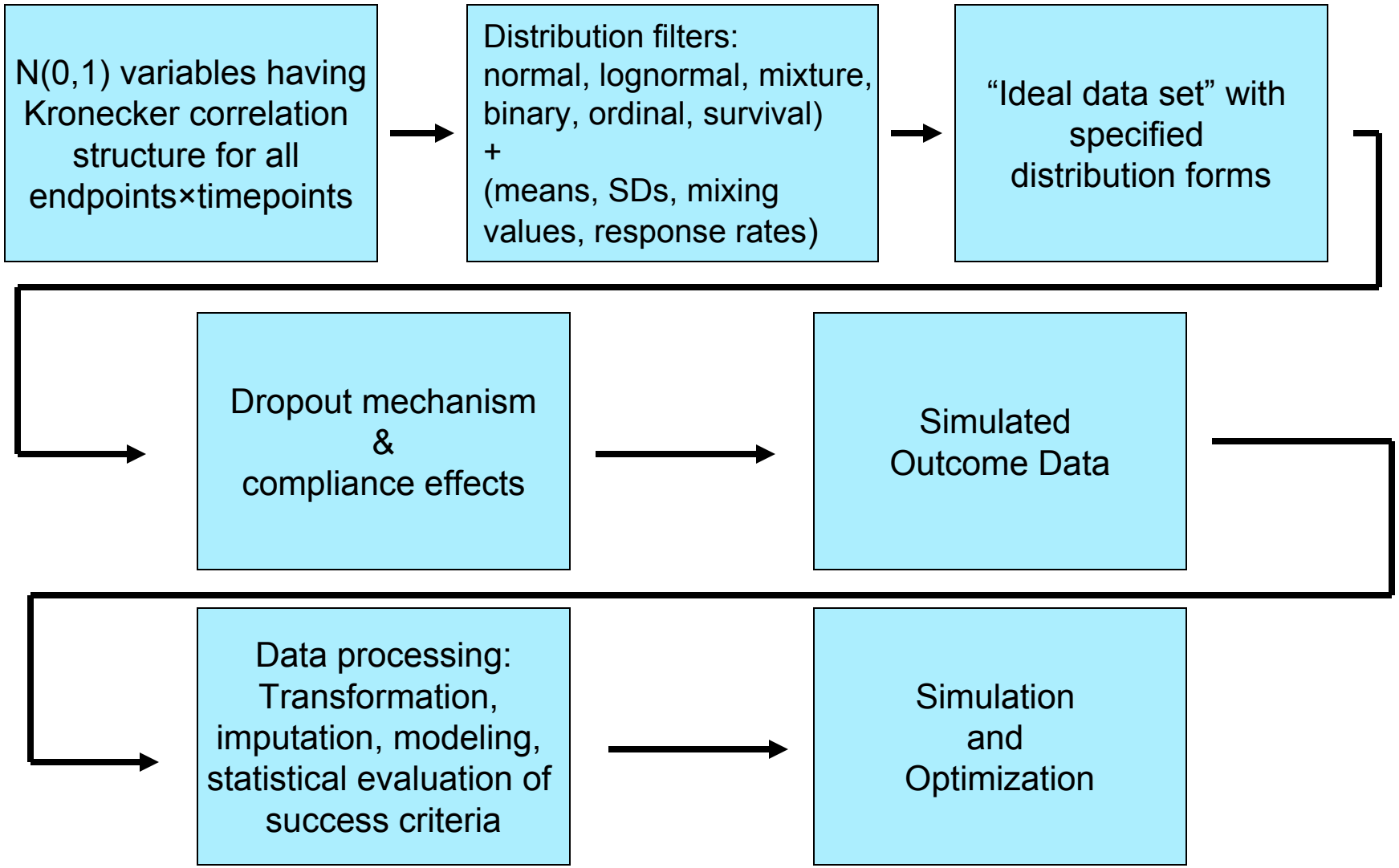
The Clinical Trials Simulation System

Overview of System



System Requirements

- The system requires at least a client (or local machine), and optionally, host machines (for grid runs).
- The system requires SAS/Windows for the client (local) machine with Version 9 or higher, (the system runs with partial functionality under Version 8), including SAS/BASE, SAS/STAT, and SAS/AF for local runs. SAS/GRAPH is desirable as well, but not necessary.
- For grid runs, SAS/CONNECT is also needed for client and hosts, and SAS/BASE, SAS/STAT are needed on the hosts, but can be in any operating system.

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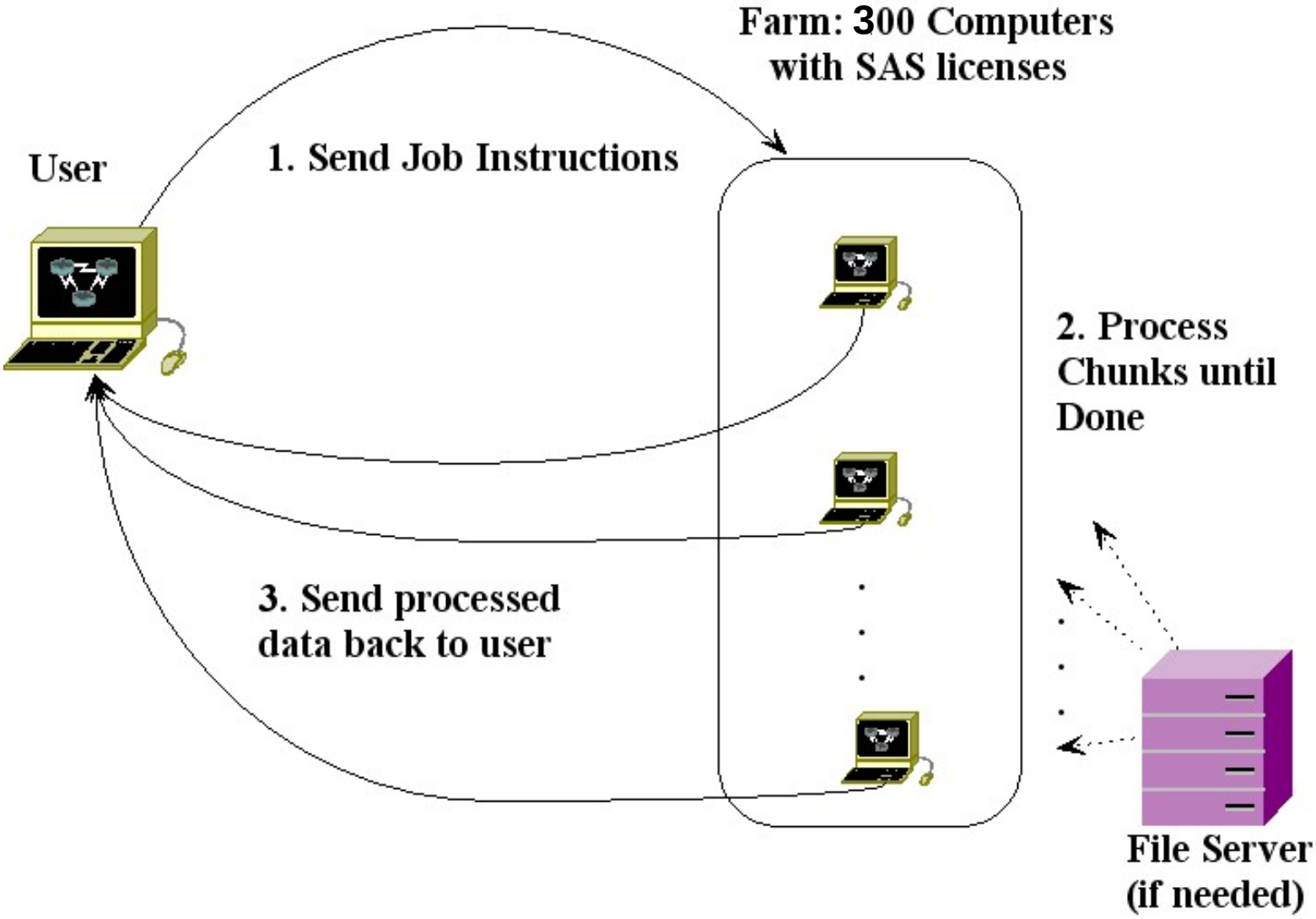
The SAS Grid


Farm: 300 Computers
with SAS licenses
User
1. Send Job Instructions
2. Process
Chunks until
Done
3. Send processed
data back to user
File Server
(if needed)

The Statistics of the System

Our Approach to Clinical Trials Simulation

- Not using PK/PD models directly
- Our goal: simulate realistic data sets
  - Flexible covariance structures
  - Flexible mean structures, inc. natural history and placebo effects
  - Compliance effects
  - Informative dropout mechanisms
  - Historical and a priori inputs
  - Emphasis on Phase II/III design
  - Statistical emphasis

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The Simulated Data

	Endpoints->	1				2				…	p			
	Timepoints->	1	2	…	t	1	2	…	t	…	1	2	…	t
PAT	Dose													
0001	Pbo	9.7	8.7	…	11.3	11.7	7.8	…	11.1	…	9.3	8.3	…	9.2
0002	Pbo	9.7	9.6	…	9.9	9.5	12.0	…	12.4	…	11.7	8.4	…	11.9
…	…	8.6	9.2	…	9.6	10.0	9.7	…	8.3	…	7.4	11.4	…	10.8
0200	High	10.7	10.3	…	9.8	10.6	10.1	…	11.9	…	10.1	10.8	…	9.1

*Simulation Model for Patient*Endpoint Data,* I

Step 1: For carryover effects, create AR(1) (ρ) series:

$Z_1 = \rho Z_0 + (1- \rho)^{½} \varepsilon_1$

…

$Z_T = \rho Z_{T-1} + (1- \rho)^{½} \varepsilon_T$

where $Z_0, \varepsilon_1, \ldots, \varepsilon_T$ are iid N(0,1)

The $\{Z_i\}$ series is first-order autoregressive with parameter ρ.

*Simulation Model for Patient*Endpoint Data,* II

Step 2: For subject effects:

$$Z_t = \theta^{1/2} S + (1 - \theta)^{1/2} \varepsilon_t \, , \; t=1,\ldots,T$$

where S is N(0,1) ind. of AR(1) $\{Z_t\}$ series.

θ = within subject correlation

*Correlation Structure Within Patient*Endpoint*

T=4 case:

$$\Sigma = \theta \begin{bmatrix} 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 \\ 1 & 1 & 1 & 1 \end{bmatrix} + (1-\theta) \begin{bmatrix} 1 & \rho & \rho^2 & \rho^3 \\ \rho & 1 & \rho & \rho^2 \\ \rho^2 & \rho & 1 & \rho \\ \rho^3 & \rho^2 & \rho & 1 \end{bmatrix}$$

θ = within subject correlation

ρ = carryover effect correlation

Correlation Between Endpoints

$$\Gamma = \begin{bmatrix} 1 & \gamma_{12} & \cdots & \gamma_{1p} \\ \gamma_{21} & 1 & \cdots & \gamma_{2p} \\ \vdots & \vdots & \ddots & \vdots \\ \gamma_{p1} & \gamma_{p2} & \cdots & 1 \end{bmatrix}$$

(p x p)

Assumed Correlation Between All Endpoints and Timepoints

$$\Gamma \otimes \Sigma = \begin{bmatrix} \Sigma & \gamma_{12}\Sigma & \cdots & \gamma_{1p}\Sigma \\ \gamma_{21}\Sigma & \Sigma & \cdots & \gamma_{2p}\Sigma \\ \vdots & \vdots & \ddots & \vdots \\ \gamma_{p1}\Sigma & \gamma_{p2}\Sigma & \cdots & \Sigma \end{bmatrix}$$

(pT x pT)

Note: Kronecker structure is assumed

Summary: Correlation Structure Inputs

θ = within subject correlation

ρ = time carryover (AR(1) parameter)

$$\Gamma = \begin{bmatrix} 1 & \gamma_{12} & \cdots & \gamma_{1p} \\ \gamma_{21} & 1 & \cdots & \gamma_{2p} \\ \vdots & \vdots & \ddots & \vdots \\ \gamma_{p1} & \gamma_{p2} & \cdots & 1 \end{bmatrix}$$

= Correlation between endpoints

Distribution Filters

- All random variables are constructed from the correlated N(0,1) :
  - Normal
  - Mixture
  - Lognormal
  - Survival
  - Binary
  - Ordinal (k)

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Mean Structure Inputs

$$\text{Define } M^{(g)} = \begin{bmatrix} \mu_1^{(g)} \\ \mu_2^{(g)} \\ \vdots \\ \mu_p^{(g)} \end{bmatrix}, \text{ where } \mu_i^{(g)} = \begin{bmatrix} \mu_{i1}^{(g)} \\ \mu_{i2}^{(g)} \\ \vdots \\ \mu_{iT}^{(g)} \end{bmatrix},$$

and $g = h, 0, 1, \ldots, G$, where

"h" denotes natural history

"0" denotes placebo

"i" denotes endpoint.

Mean Structure $M^{(g)}$ Specification

- Can come from
  - PK/PD models
  - Early phase data
  - Studies on similar compounds
- To simplify – specify a small number of x-coordinates, specify means for each group, use piecewise linear interpolation

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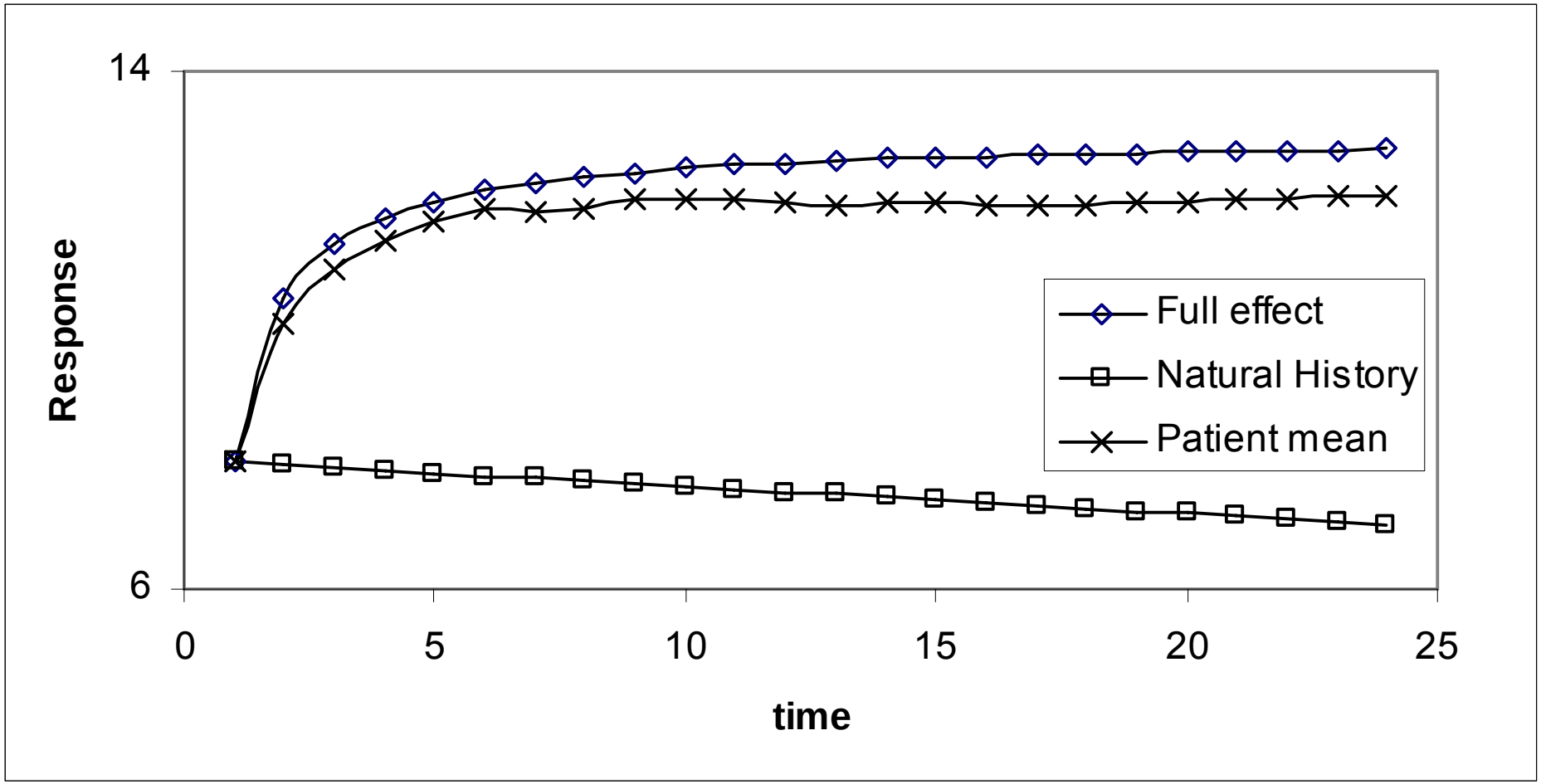
Mean Structures



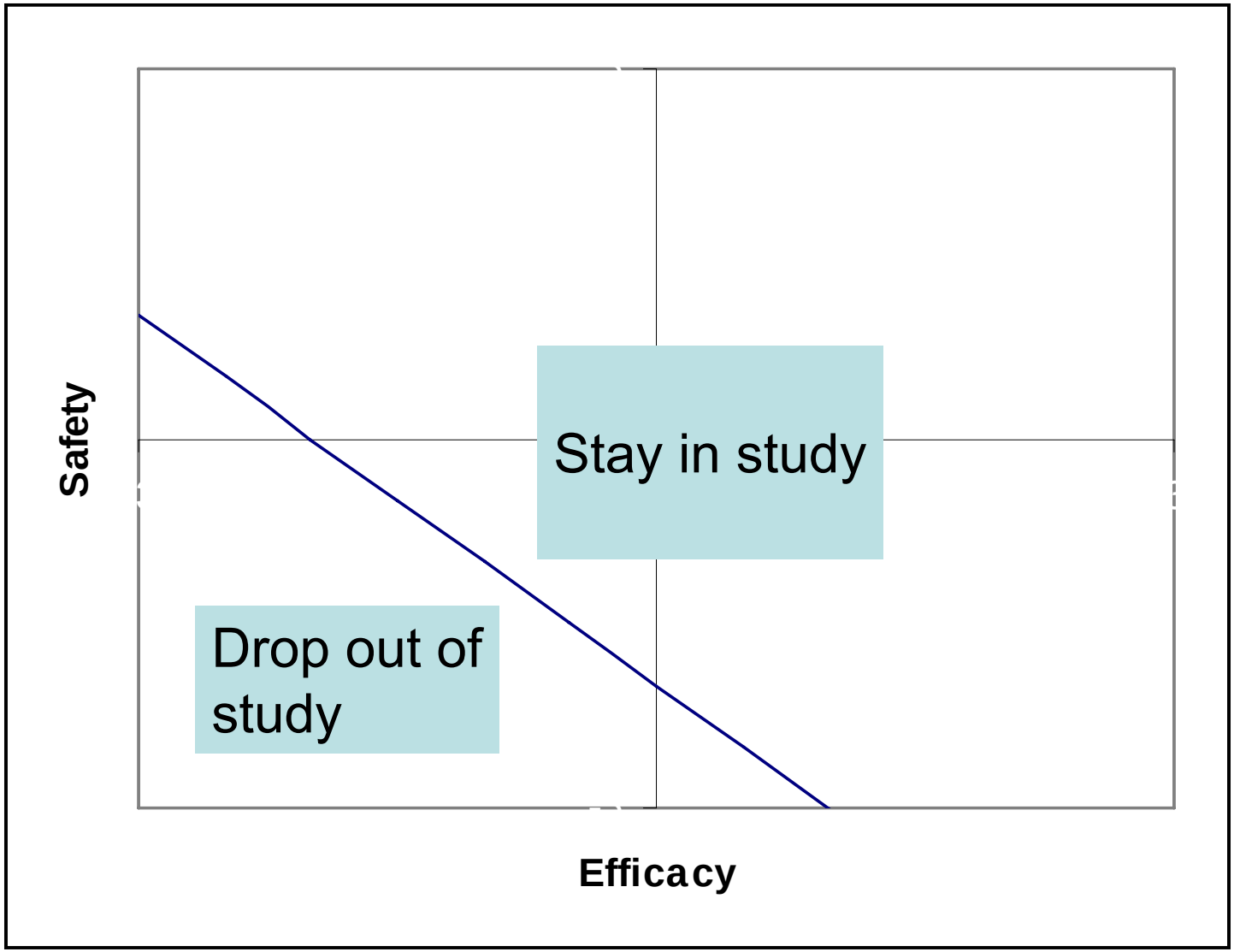
Mixture Distribution

- For each endpoint i, input contamination fraction p_i, and ratio r_i of contaminated to normal stdevs.

$$Z_{igt} \leftarrow I(U \geq p_i) Z_{igt} / (1 - p_i + p_i r_i^2)^{1/2} + I(U < p_i) r_i Z_{igt} / (1 - p_i + p_i r_i^2)^{1/2}$$

- Otherwise same as for normal
- Correlations maintained among contaminated variables with common fractions, otherwise attenuated; means and stddevs identical

Discontinuation Model



Misery Indices

Safety Misery Index

S_t = average of safety endpoints[1] at time t

Efficacy Misery Index

E_t = average of efficacy endpoints[1] at time t

Combined Index

$I_t = (\text{safetyweight})*S_t + (1\text{-safetyweight})*E_t$

[1] All using the basic variables, ***reverse*** coded so that higher is worse

Cumulative Misery Index

Cumulative misery index is defined recursively as

$CI_1 = I_1$
$CI_2 = I_2 + (1\text{-recency})*CL_1$
…
$CI_t = I_t + (1\text{-recency})*CL_{t-1}$
…

Recency = 1 implies local index
Recency = 0 implies cumulative index
Recency between 0 and 1 weights recent history higher

The Dropout Model

- Dropout thresholds p_0, p_h, p_1,…,p_G are specified
- A given patient is in group g, and has data at time points t = 0,1,…,T.
- As soon as CI_t exceeds the 1- p_g quantile of the distribution of CI_t, the patient drops out.

Noncompliance Data

- Within-Patient Probit model for % compliance
- Generate $Z_t = \theta^{1/2} Z_0 + (1- \theta)^{1/2} \varepsilon_t$, t=1,…,T, with Z_0, $\varepsilon_1,\ldots, \varepsilon_T$ iid N(0,1)
- $U_t = \phi^{1/2} Z_t - (1-\phi)^{1/2} CI_t$; ϕ = correlation of random noncompliance with cumulative misery index
- Compliance = $p_t = \Phi(a+bU_t)$
- a, b, chosen to match user-specified median and 10^{th} percentile of compliance
- Allowed to differ by treatment group

Noncompliance Model

- Holford and Peace (1992)
- Lee et al. (2003)
- Placebo group is also regressed toward natural history by noncompliance. If natural history is not specified, the assumption is that the dose groups regress towards placebo

Outputs Goals

- **Analysis**
  - Jonckheere-Terpstra trend analysis
  - Chi-square
  - Cochran-Armitage
  - Cox proportional hazards analysis
  - ANOVA or ANCOVA followed by LS means pair-wise comparison with different multiple comparison adjustments
  - Resampling
  - Bayesian
- **Display**
  - Summary of rejecting and accepting the null hypotheses
  - Graph of power function using a series of sample sizes
  - Summary of basic statistics
  - Summary of simulation conditions

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Technical Report Containing Mathematical Details

Clinical Trials Simulation: A Statistical Approach

Peter H. Westfall[1], Kuenhi Tsai[2], Stephan Ogenstad[3], Alin Tomoiaga[1], Miles Dunn[2], Yonggang Lu[1]

[1] Texas Tech University

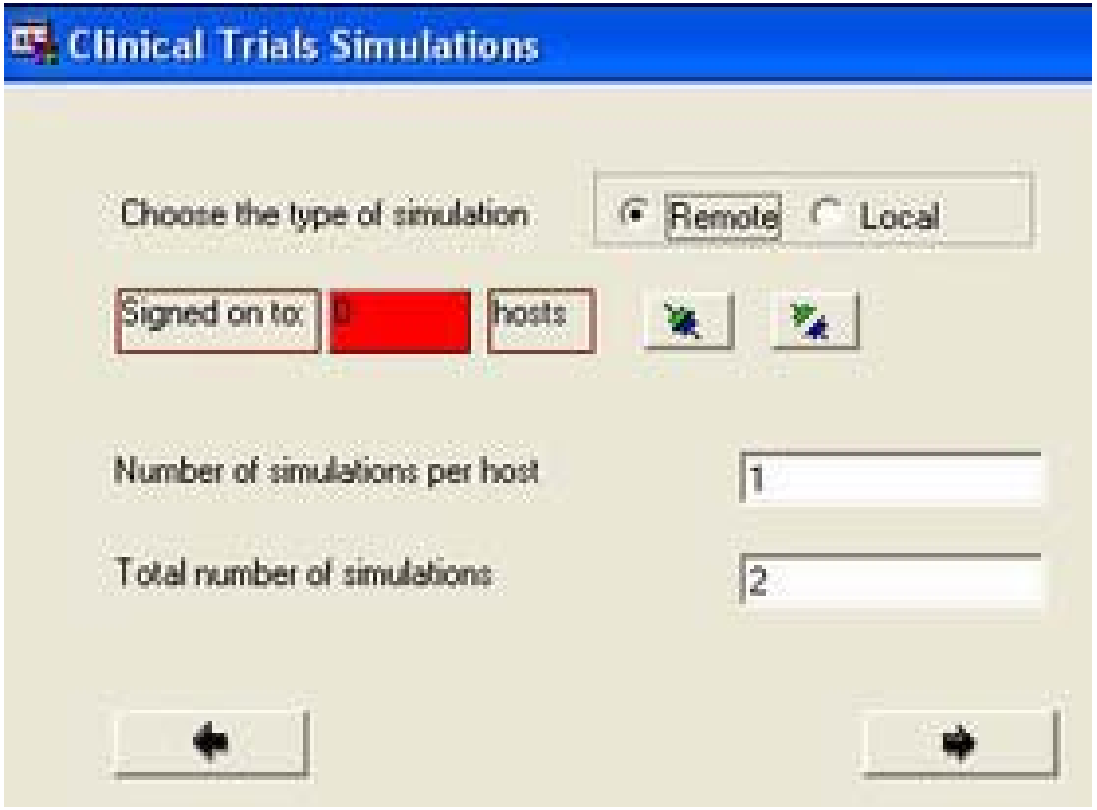
[2] Vertex Pharmaceuticals

[3] Statogen Consulting, LLC

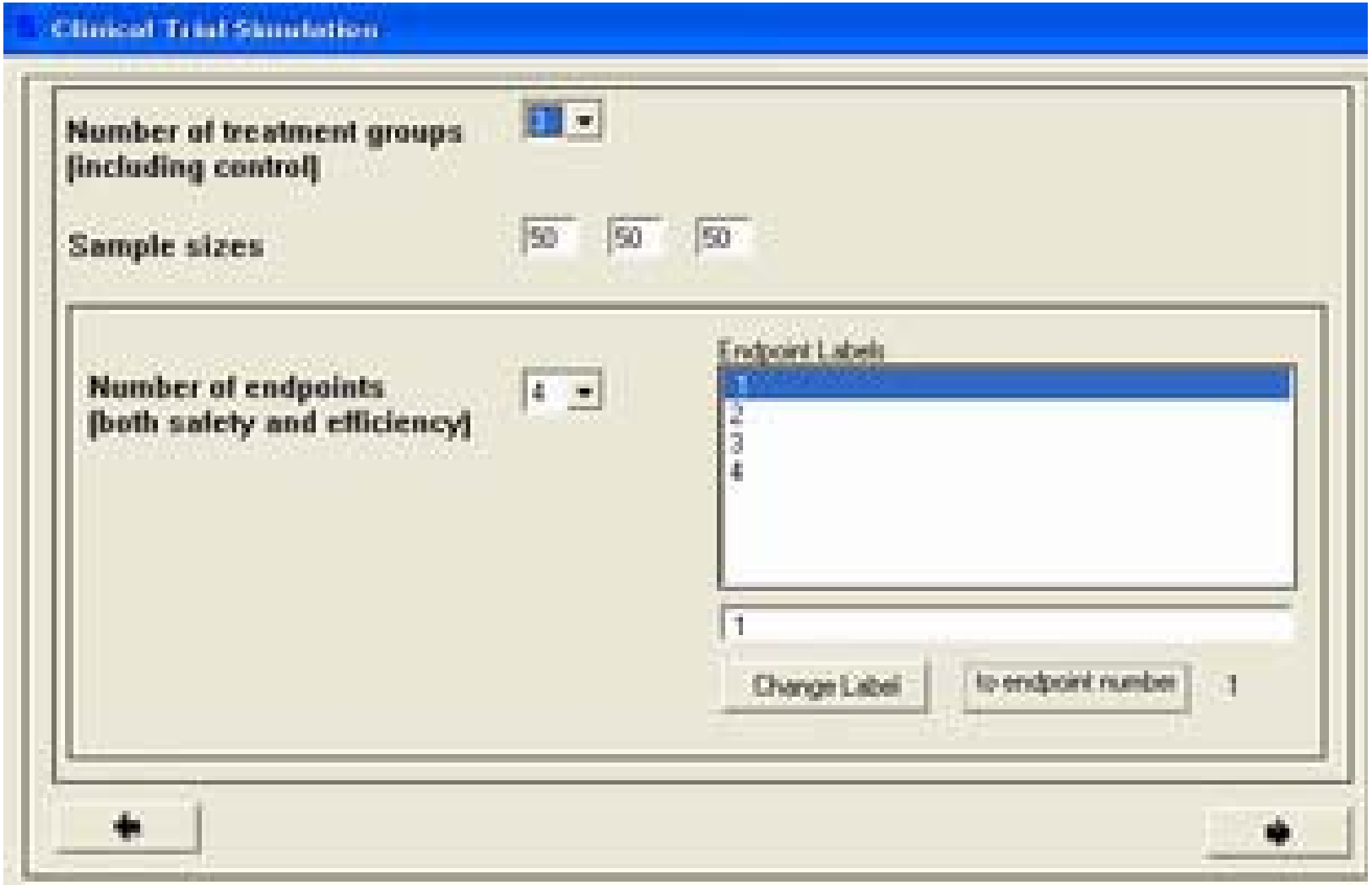
Running the Application

Frame 1: Starting the system

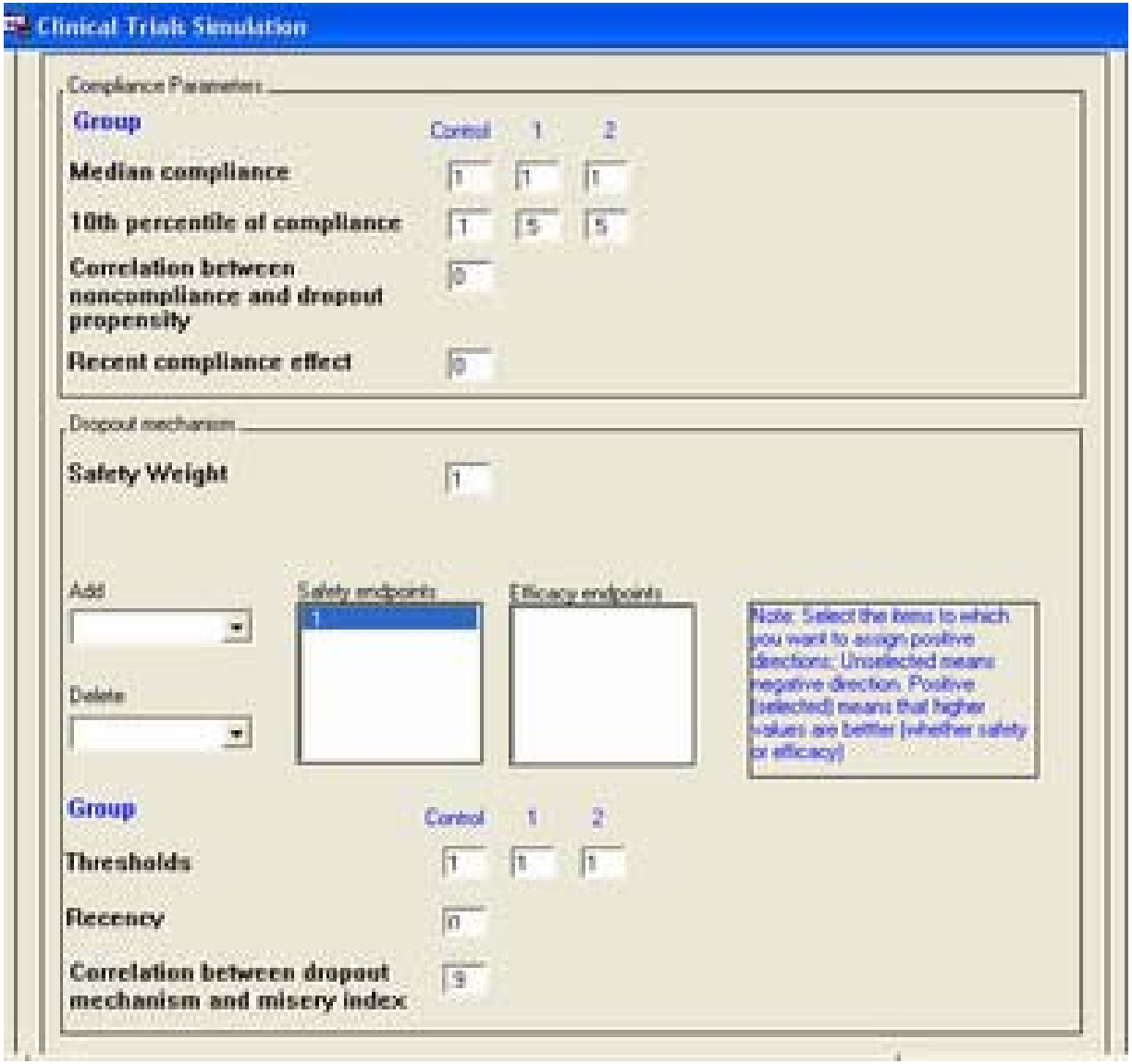
Frame 2: Local or grid runs



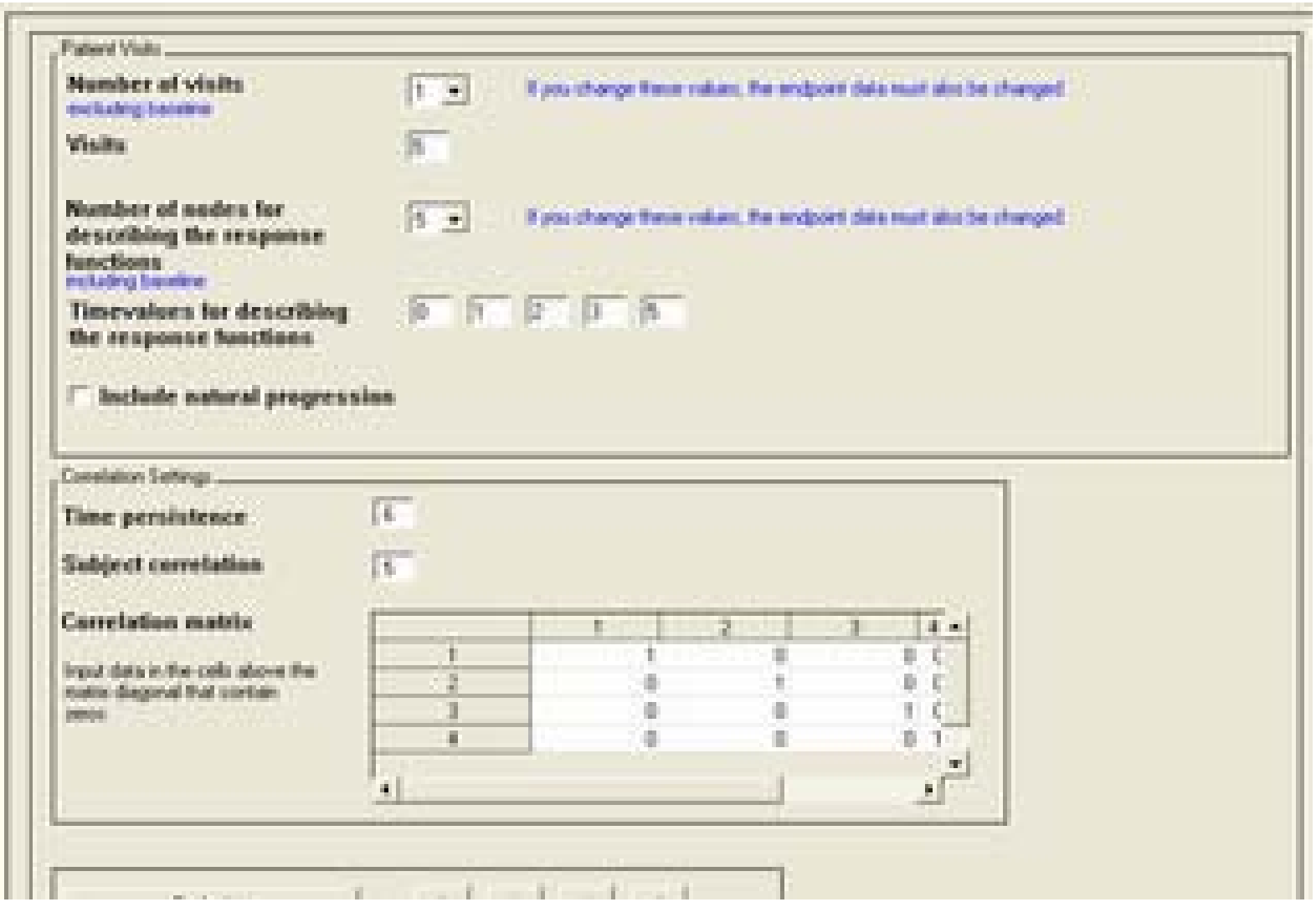
Frame 3: Input of Clinical Trial Parameters



Frame 4: Compliance and Dropout mechanisms

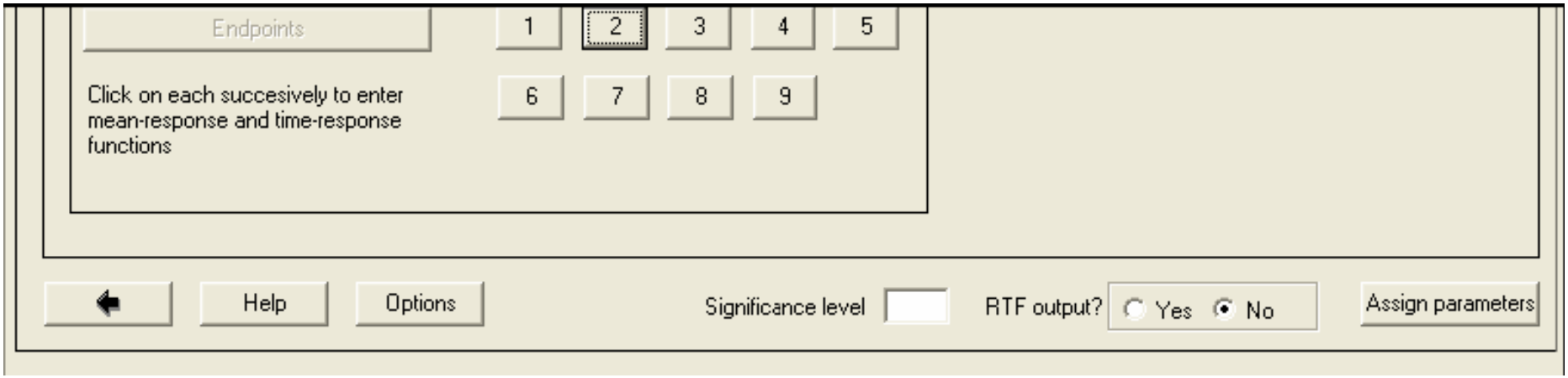


Frame 5: Number of timepoints, endpoint and timepoint correlation data



Frame 6: Endpoint Specifications

Frame 5': Final actions



Examples

Examples 1 - 3

The following three examples were analyzed using the system, and show a sample of what is possible. The scope of applications is much broader than the small sampling shown here.

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Sample Size Allocation

- Rheumatoid arthritis drug, with the binary outcome ACR20 as the primary endpoint, and Control, Low, Mid, and High doses.
- ACR20 response rates are 30%, 50%, 60% and 70%, respectively, and that patient dropout rates are 5%, 10%, 15%, and 20%, respectively.
- Chi-Square Dose/placebo tests, using the fixed sequence multiple comparisons method (High dose first, then Mid dose, then Low dose, tested in order until one fails to achieve significance.)
- Total number of patients is 200, and the question is, how to allocate them among the groups?
- Elements that make this problem require simulation (rather than analytical results)
  - the use of Chi-Square tests, whose mathematical distributions are asymptotic rather than exact in finite samples,
  - the dropout issue, and
  - the use of fixed sequence tests, whose power functions depend on joint distributions rather than marginal distributions.

Using the System

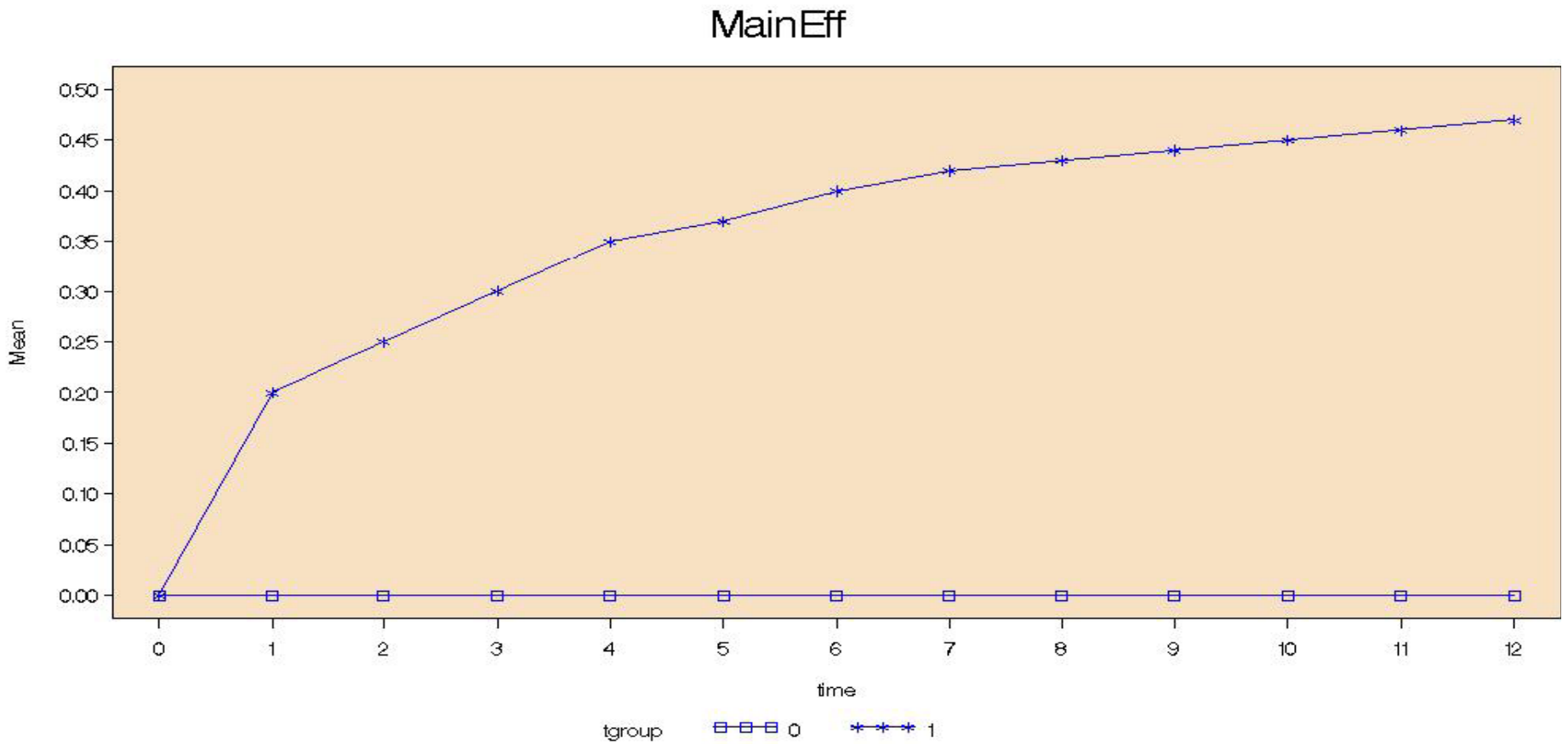
20,000 simulated clinical trials per design (using the grid implementation)

Design	High Dose	Med Dose	Low Dose
50,50,50,50	0.973	0.816	0.465
101,33,33,33	0.966	0.800	0.448
95,30,35,40	0.981	0.822	0.426
80,40,40,40	0.977	0.835	0.480
80,35,40,45	0.985	0.837	0.452
74,42,42,42	0.976	0.834	0.484

Choice of Test

Design	O'Brien	ACR_{20}
50,50	.60	.41
70,70	.86	.40
100,100	.98	.58

Choice of Design, Test, and Duration of Study



Type of Analysis

Design	AOV	ANCOVA Mean	ANCOVA Median	Difference Mean	Difference Median	K-W	K-W Diff Mean	K-W Diff Median
12 wks 30, 30	0.41	0.55	0.54	0.48	0.47	0.58	0.67	0.65
12 wks 50, 50	0.57	0.73	0.72	0.67	0.64	0.80	0.87	0.86
12 wks 100, 100	0.83	094	0.93	0.90	0.89	0.97	0.99	0.99
8 wks 30, 30	0.36	049	0.48	0.43	0.41	0.51	0.59	0.57
8 wks 50, 50	0.51	0.67	0.66	0.59	0.58	0.73	0.82	0.80
8 wks 100, 100	0.78	0.90	0.90	0.86	0.84	0.95	0.98	0.98

Example 4: A Complex Input Simulation

- 9 end points
  - 1 mixture, 1 survival, 2 ordinal, 5 binary
  - All endpoints are correlated
- 12 time points
- 2 groups
- 50 subjects in each group
- 1000 simulations

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CPU Time

Site	# of computers	Computer features	Elapsed time (min:second)	Cumulative working time
Vertex	4	3 GHZ CPU 4 GB RAM	2:23	9:03
Vertex	1	3 GHZ CPU 4 GB RAM	9:41	9:38
Texas Tech	4	2.8 GHZ CPU 1 GB RAM	4:40	18:03
Texas Tech	1	2.8 GHZ CPU 1 GB RAM	15:45	15:46
Texas Tech	20	2.8 GHZ CPU 1 GB RAM	1:19	18:03

Note: Elapsed time including waiting time

Conclusion

- The industry needs to be less risk-adverse to innovation
- Clinical trial simulations is a collaborative effort and one of the necessities, of great promise, to rational drug development in a true sense

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Thank You!

sogenstad@statogen-consulting.com

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References

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Additional Slides

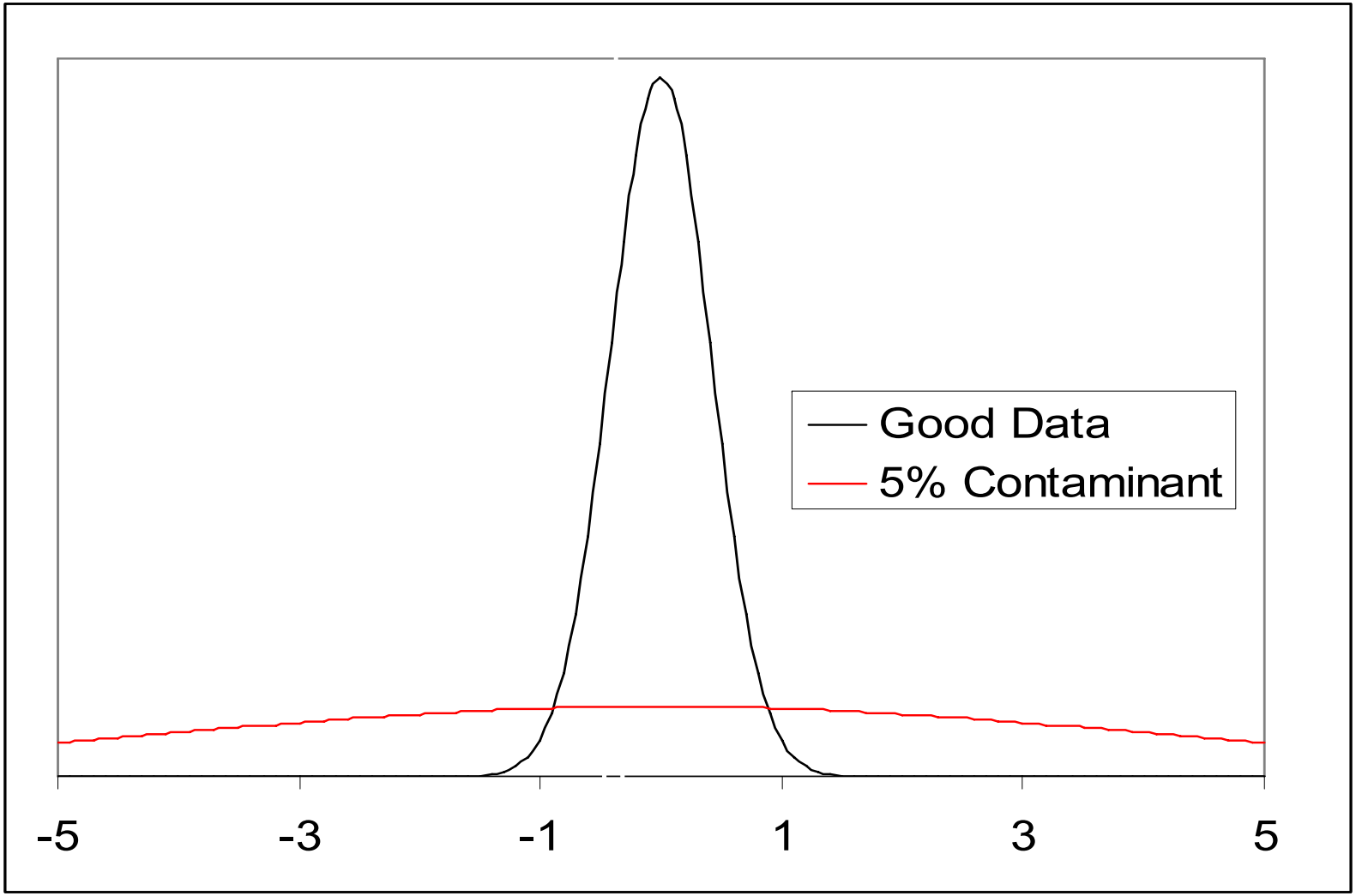
Normal Distribution

$$\text{Input } \boldsymbol{\sigma} = \begin{bmatrix} \sigma_1 \\ \sigma_2 \\ \vdots \\ \sigma_p \end{bmatrix}, \text{ where } \sigma_i = \begin{bmatrix} \sigma_{i1} \\ \sigma_{i2} \\ \vdots \\ \sigma_{iT} \end{bmatrix}.$$

$$\text{Let } \mathrm{X} = \boldsymbol{\sigma} \otimes \mathrm{W} = \begin{bmatrix} \sigma_1 \otimes \mathrm{W}_1 \\ \sigma_2 \otimes \mathrm{W}_2 \\ \vdots \\ \sigma_p \otimes \mathrm{W}_\mathrm{p} \end{bmatrix}$$

$$\text{Then } Cov(\mathrm{X}) = Diag(\boldsymbol{\sigma})(\Gamma \otimes \Sigma)Diag(\boldsymbol{\sigma}).$$

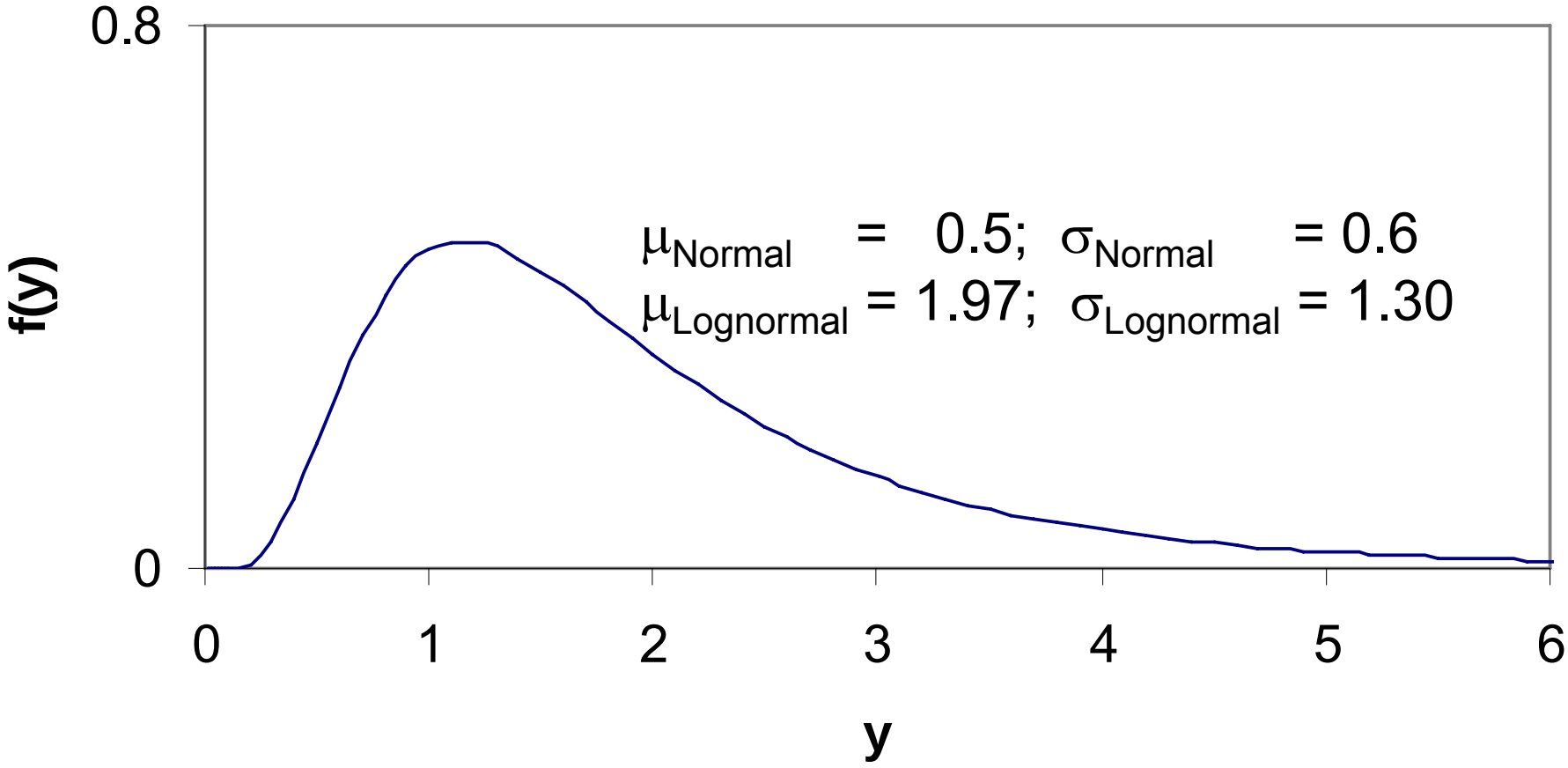
Mixture Distribution: 5% contaminant; StDev Ratio = 10
Mixture pdf: Mean = 0, SD = 1, Kurtosis = 39.45



Lognormal Distribution

- For endpoint i, group g, timepoint t, input median values m_{igt}, and baseline StdDev s_i for actual data
- $W_{igt} \rightarrow \exp(m_{igt} + \sigma_i' W_{igt})$
- σ_i' chosen so that StdDev{$\exp(m_{ig0} + \sigma_i' W)$} = s_i
- Input correlations refer to logged, not actual data

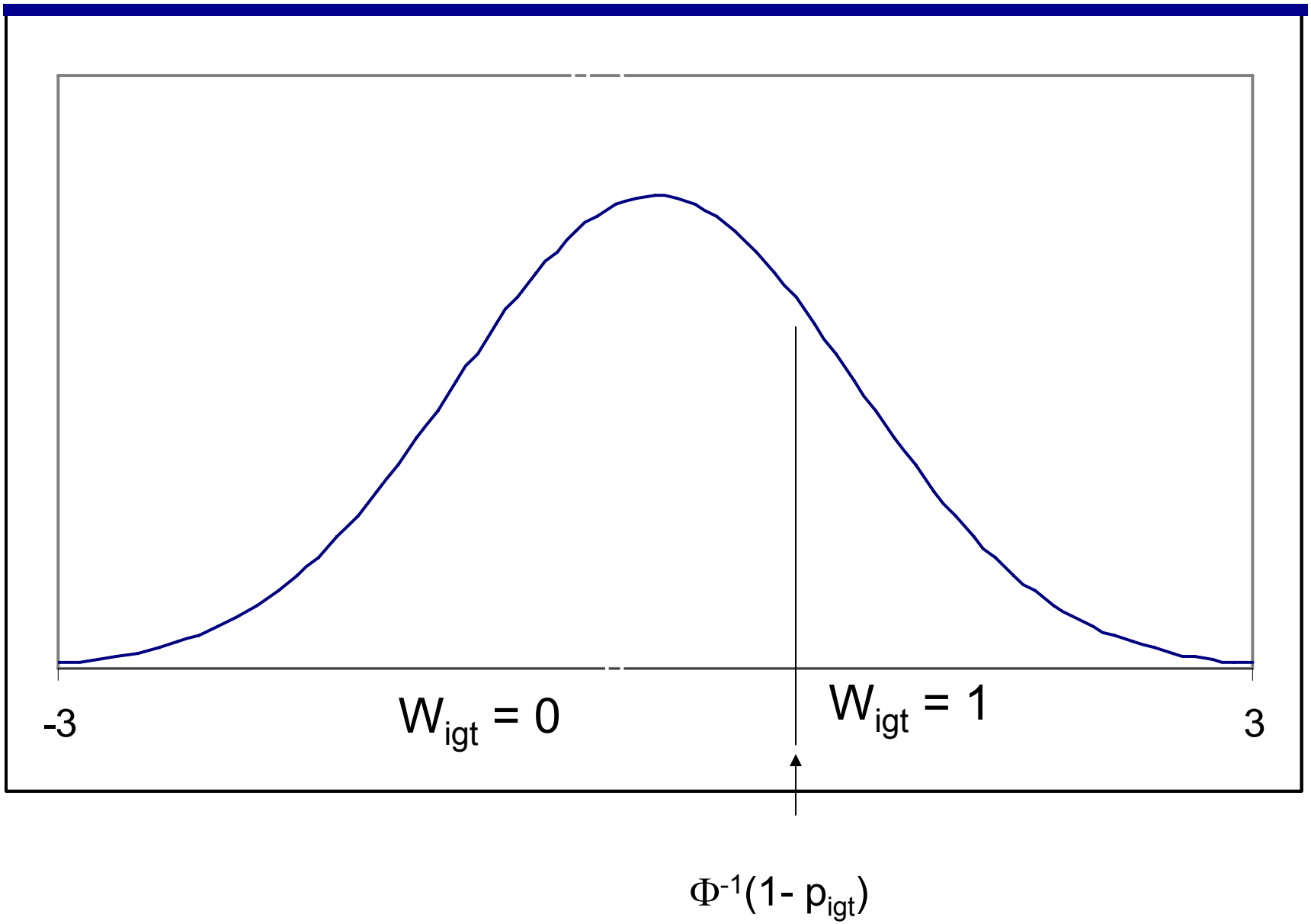
The Lognormal Density Function



Binary Distribution

- Input probabilities p_{igt} ; thresholds are $t_{igt} = \Phi^{-1}(1 - p_{igt})$
- $W_{igt} \rightarrow I(W_{igt} > t_{igt})$
- Correlations refer to tetrachoric correlations

Binary Model

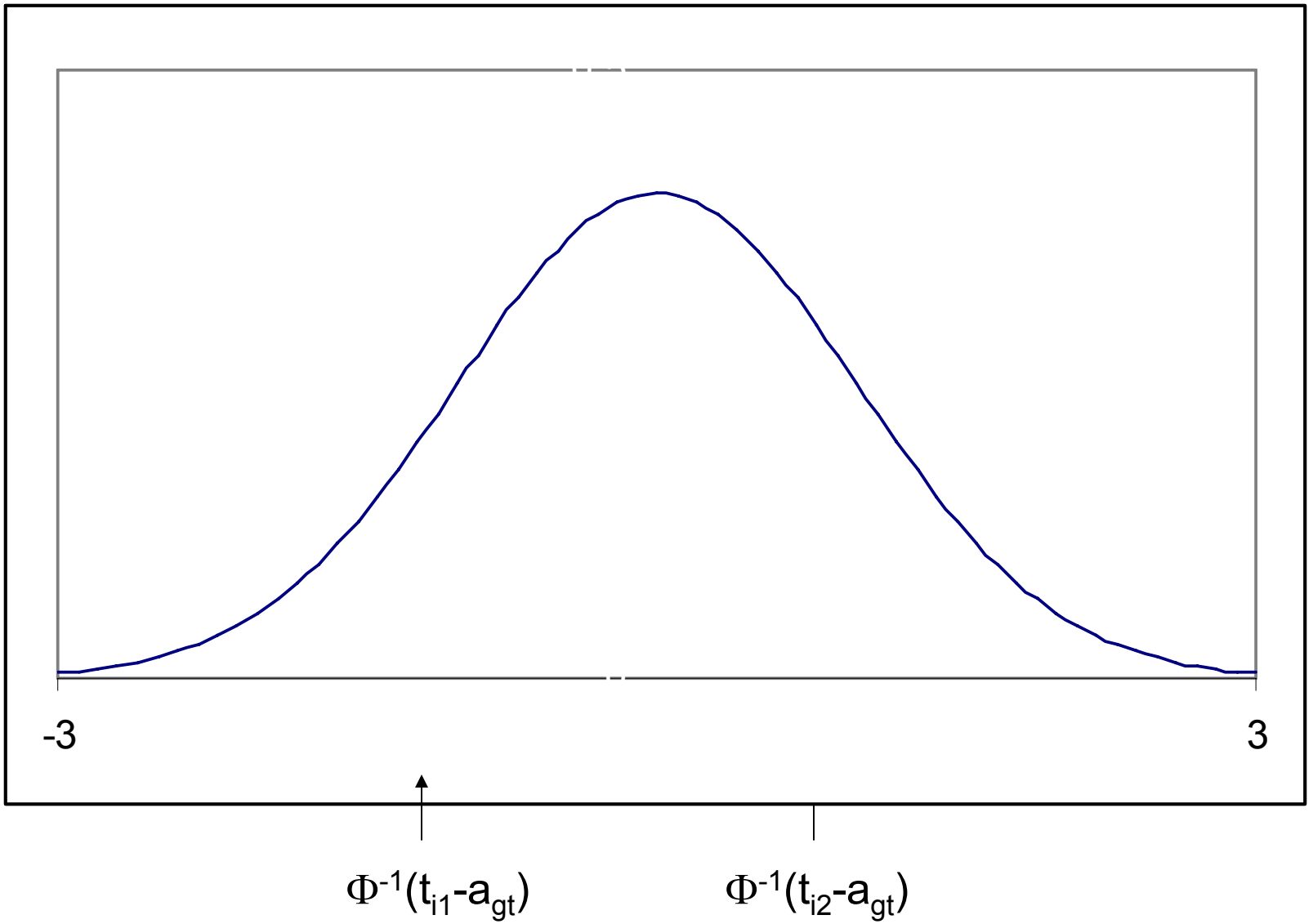


Ordinal Distribution (k levels)

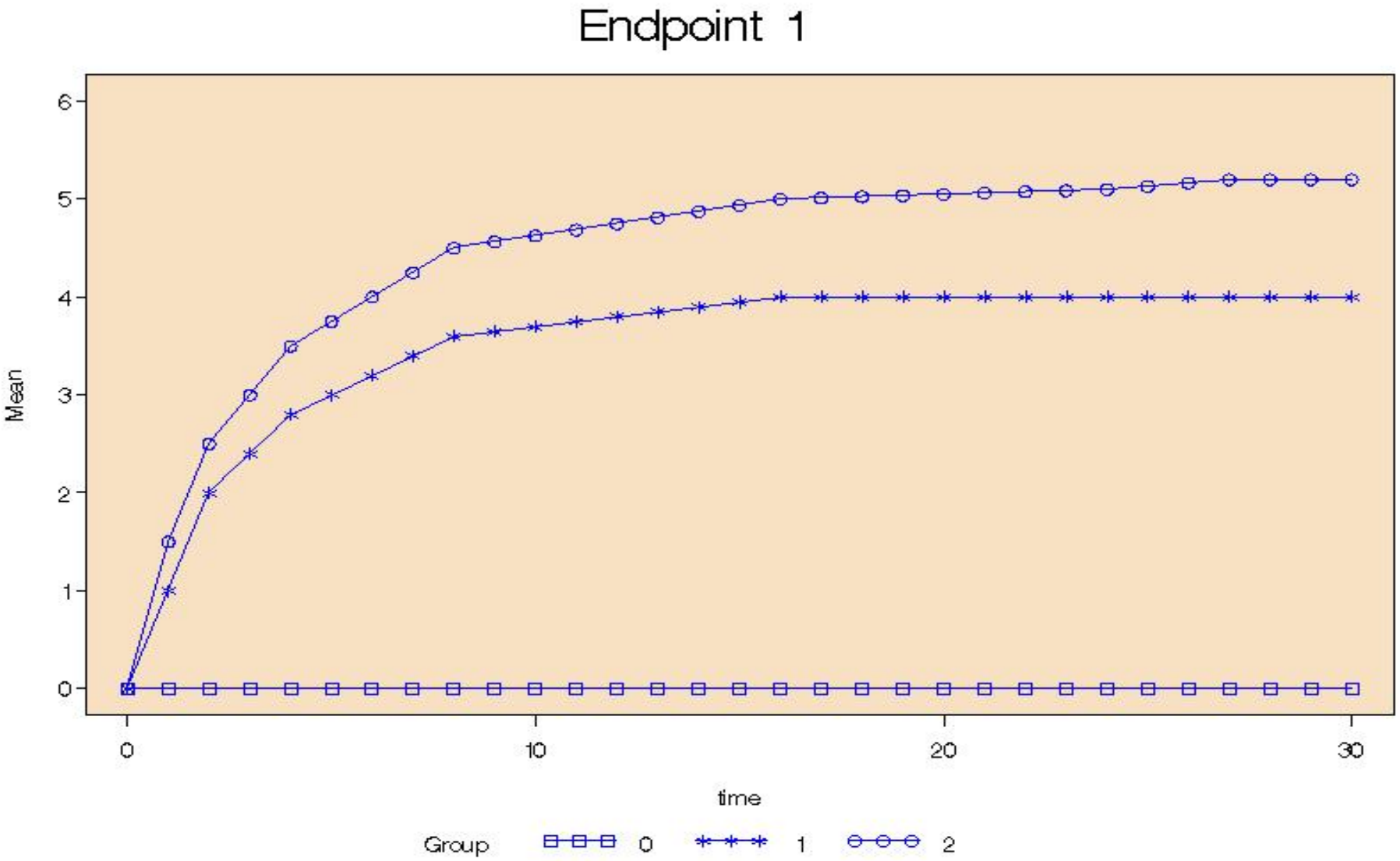
- Input means m_{igt} and baseline probabilities $p_{i1},\ldots,p_{ik}$ $(m_{ig0} = 1\times p_{i1}+\ldots+k \times p_{ik})$.
- Baseline thresholds are $t_{il}=\Phi^{-1}(p_{i1}+\ldots+p_{il})$, $l=1,\ldots,k-1$.
- Solve for location shifts a_{gt}:

  $m_{igt} = 1\times\Phi(t_{i1}- a_{gt}) +\ldots+ k\times\{1-\Phi(t_{i,k-1}- a_{gt})\}$
- $W_{igt} \rightarrow 1 + I(W_{igt} > t_{i1} -a_{gt}) + \ldots+ I(W_{igt} > t_{i,k-1}- a_{gt})$
- Correlations refer to polychoric correlations

Ordinal Model



Example: Piecewise Linear Mean Construction



Example 5

Estimating Treatment Effect in Clinical Trials with Disease Dependant Non-Compliance

Non-Compliance in General

- Definition: failure of patients to take medicines in their prescribed manner
- Consequences in health care
  - Cost US economy $100 billion per year (Forum on patient compliance 2002)
  - Increase morbidity and mortality
  - Non-compliance ranges from 20% to 80% depending on the type of treatment (Jaret 2001)

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Non-Compliance in Clinical Trials

- Departure from protocol
- Often better than that seen in general clinical practice
- Affected by factors such as the duration of the treatment, the number of times a drug has to be taken per day, literacy, and potential side effects

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Goal

- Investigate the non-compliance impact on treatment effect on 3 different therapeutic areas based on published PD models or data

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Characteristics of Diseases

- Alzheimer: fast progressing disease
- Rheumatoid Arthritis: slow progressing disease and strong placebo effect
- HIV: fast progressing and possible resistance to drug

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Assuming Compliance Effect

- Alzheimer (AL): Regress to natural disease
- Rheumatoid Arthritis (RA): Regress to placebo
- HIV: When compliance is low, regress to no treatment effect, due to viral resistance

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Simulation Design for 3 Diseases

- AL: 2 groups (placebo and treatment), regress to natural disease, same compliance rates
- RA: 2 groups (placebo and treatment), regress to placebo, same compliance rates
- HIV: 2 groups (QD and BID), regress to natural disease, different compliance rates

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What Expected from Simulations in Comparing Two Treatment Groups

Incorporating the compliance as covariate

- AL: compliance effect may not be significant
- RA: compliance effect may not be significant
- HIV: compliance effect may be significant

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Alzheimer

- Pharmacodynamic (PD) and pharmacokinetic (PK) model (Holford and Peace 1992)
- Alzheimer disease assessment scale (ADASC)
- Disease Progression Model

S(t) = Baseline + Progression with time + PD(Active Drug PK) + PD(Placebo PK)

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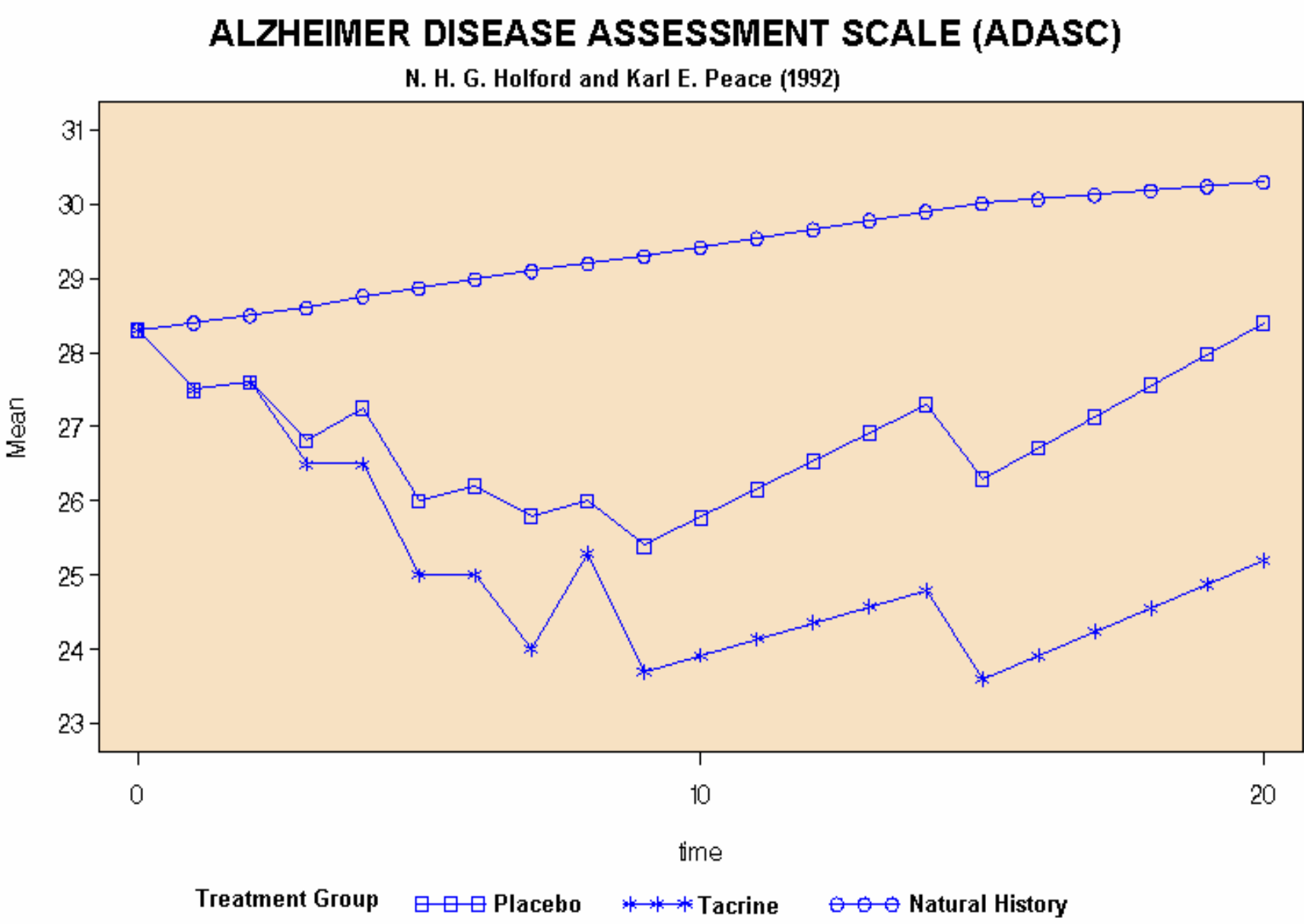
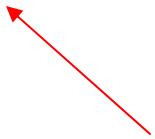

ALZHEIMER DISEASE ASSESSMENT SCALE (ADASC)
N. H. G. Holford and Karl E. Peace (1992)
Mean
31
30
29
28
27
26
25
24
23
0
10
20
time
Treatment Group
Placebo
Tacrine
Natural History

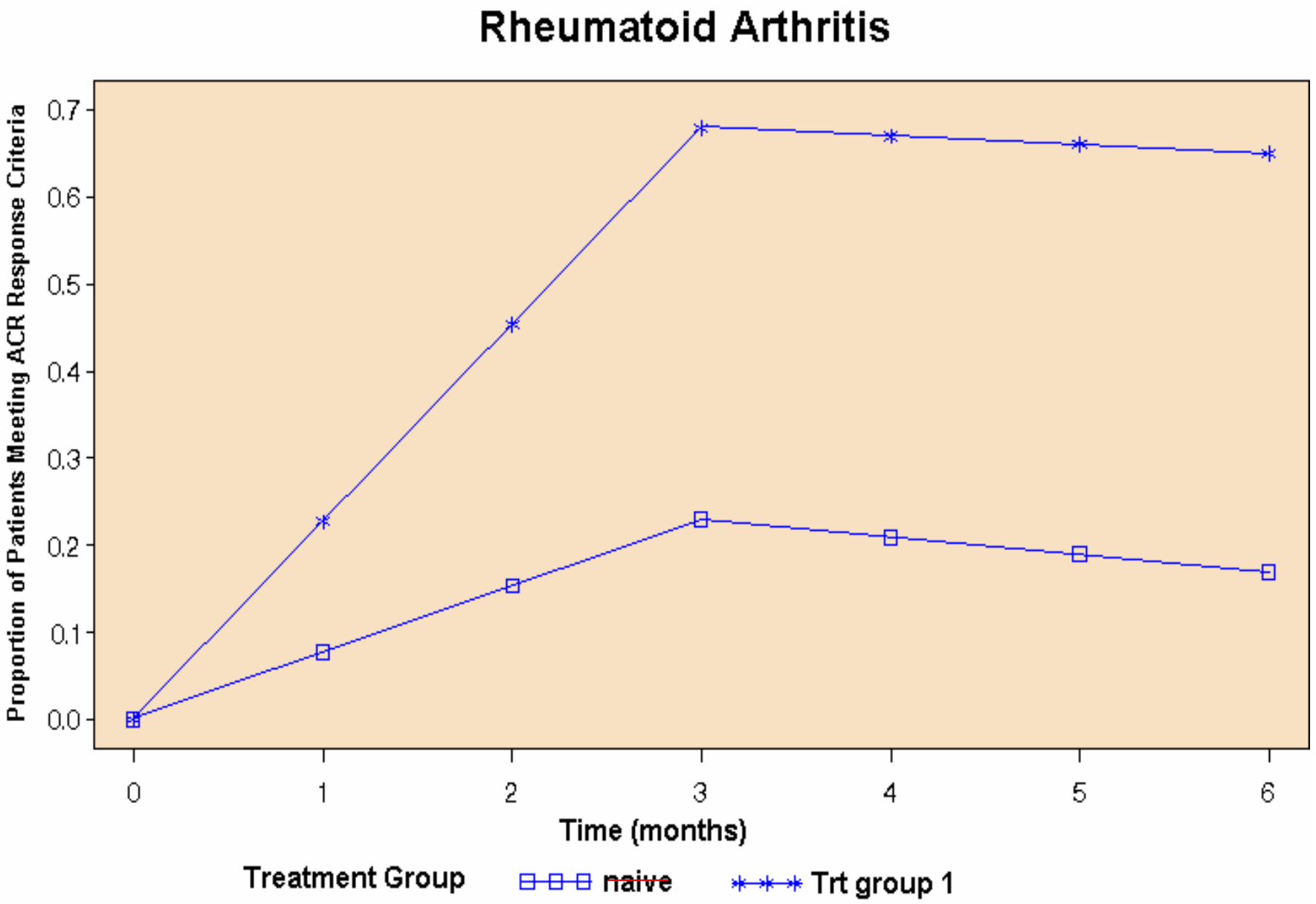
Rheumatoid Arthritis

- Pharmacodynamic (PD) and pharmacokinetic (PK) model (Lee et al. 2003)
- Response: probability to achieving ACR20 (p)
- A logistic model contains exposure and time

$$\text{Logit}(p) = \text{Ln}\,(p/(1-p)) = f(\text{exposure, time}) + \text{error}$$

$$f(\text{exposure, time}) = f_p\ (\text{placebo effect}) + f_e\ (\text{treatment effect})$$




Rheumatoid Arthritis
Proportion of Patients Meeting ACR Response Criteria
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0
1
2
3
4
5
6
Time (months)
Treatment Group
naive
Trt group 1

Placebo

HIV

- Based on a HIV short term study (Oette et al. 2006)
- Assume the same doses per day, but two treatment regimens (once per day vs. q12) with different compliance rates

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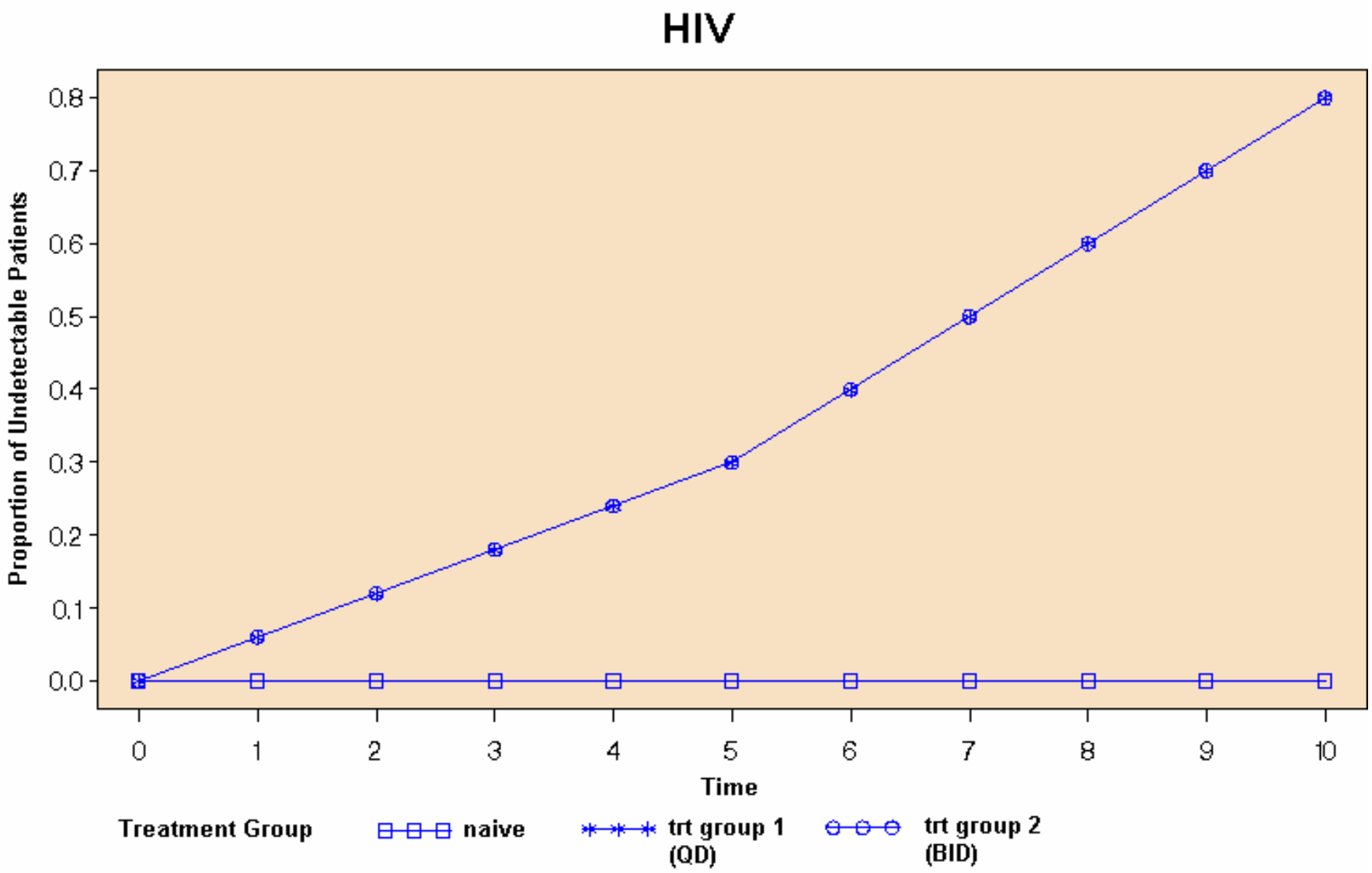
HIV
Proportion of Undetectable Patients
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0.7
0.8
0
1
2
3
4
5
6
7
8
9
10
Time
Treatment Group
naive
trt group 1
(QD)
trt group 2
(BID)

Simulation Models

- Timepoints
  - AR(1) (ρ) and subject effect for within-subject data
- Compliance
  - Percentage determined using a random-effects within-patient model
  - Noncompliance regresses the patient response toward natural history or placebo

Results of Simulations in Alzheimer

Alzheimer 1000 Simulations (N=20)	
Compliance	Power
Perfect compliance	0.908
Median compliance = 0.95 and 10% = 0.35	
Analysis without compliance (continuous)	0.683
Analysis with compliance	0.711

Alzheimer 1000 Simulations (N=29)	
Compliance	Power
Perfect compliance	0.98
Median compliance = 0.95 and 10% = 0.35	
Analysis without compliance (continuous)	0.874
Analysis with compliance	0.887

Results of Simulations in Rheumatoid Arthritis

Rheumatoid Arthritis 1000 Simulations (N=20)	
Compliance	**Power**
Perfect compliance	0.98
Median compliance = 0.95 and 10% = 0.35	
Analysis without compliance (continuous)	0.713
Analysis with compliance	0.726

Results of Simulations in HIV

(Null Hypothesis Testing with 1000 Simulations)
Median 0.95 and 10% = 0.35 vs Median 0.95 and 10% = 0.75

Comparison b/w 2 Groups	P-Value < 0.05
Compliance not in analysis	21.30%
Compliance as a continuous covariate	4.20%
Compliance as a covariate using 0.7 defining bad and good	**5%**
Compliance as a covariate using 0.8 defining bad and good	4.80%
Compliance as a covariate using 0.9 defining bad and good	10.30%

Results

- Non-compliance affects the power, but in different levels depending upon the disease progress and sample size
- When two groups with the same non-compliance rates, the power is reduced. Analyzing these data with the compliance as a covariate cannot reach the same power
- When two groups with different compliance rates and the same response rates, analyzing the data with the compliance as a covariate can reach the same power
- Traditionally, we measure a single compliance rate for a subject and categorically class it. We have to select the category carefully and meaningfully

Efficient Simulation of Data with Kronecker Covariance Structure

Let $V_1, \ldots, V_p$ be independent (Tx1) vectors generated according to subject effect/carryover effect model. Compute

$$W_1 = c_{11} V_1 + c_{12} V_2 + \ldots + c_{1p} V_p$$
$$W_2 = c_{21} V_1 + c_{22} V_2 + \ldots + c_{2p} V_p$$
$$\ldots$$
$$W_p = c_{p1} V_1 + c_{p2} V_2 + \ldots + c_{pp} V_p$$

$$Cov \begin{bmatrix} W_1 \\ \vdots \\ W_p \end{bmatrix} = \Gamma \otimes \Sigma$$

Where $C = \{c_{ij}\}$ satisfies $CC' = \Gamma$. Then

The "Ideal" Data Set

For a random patient in group g, g = 0,…, G

$$Y = M^{(g)} + X = \begin{bmatrix} \mu_1^{(g)} + X_1 \\ \mu_2^{(g)} + X_2 \\ \vdots \\ \mu_p^{(g)} + X_p \end{bmatrix}$$

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