Model-Based Drug Development

Russell Reeve, Innovation, Quintiles

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BASS 2012

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Navigating the new health
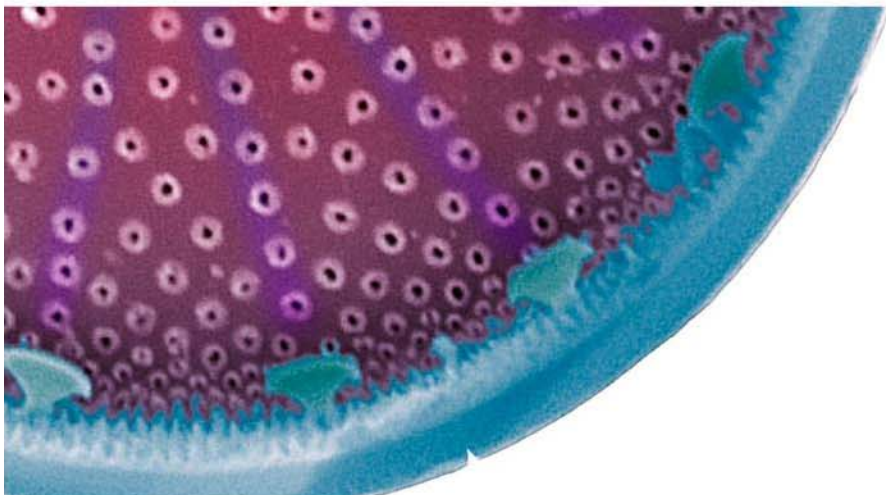
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Disclaimer and Acknowledgments

– Disclaimer

- Views presented herein are mine alone, and do not necessarily reflect those of Quintiles

- All examples presented have been modified (new endpoints, new indication, etc.) to protect client confidentiality

– Acknowledgments

- Would like to share my appreciation for my colleagues **James Powers, Seth Berry and Michael O'Kelly** who agreed to let me share their case studies

Talk Outline

– Traditional drug development

– Industry trends that make traditional development inadmissible

– Model-based drug development (MBDD)

- What is it?
- Some examples applied to specific trial design
- Work we are doing to establish its benefit on drug development programs

– Organizational issues with moving to the MBDD paradigm
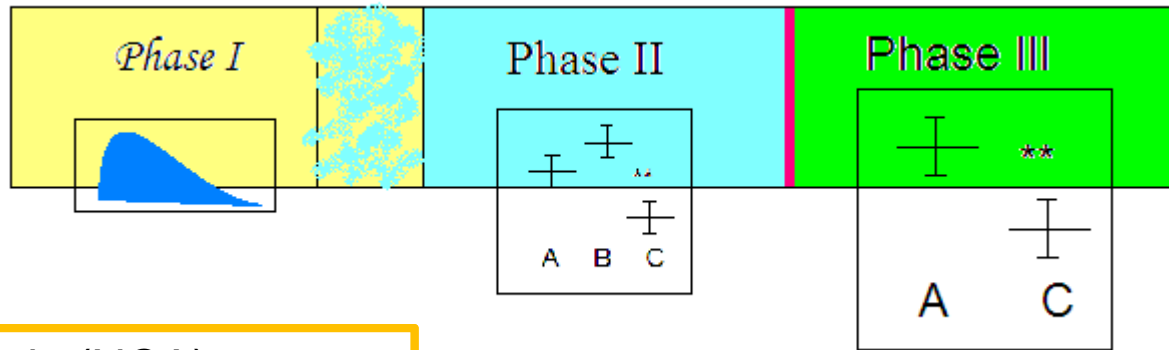
– Questions and your comments
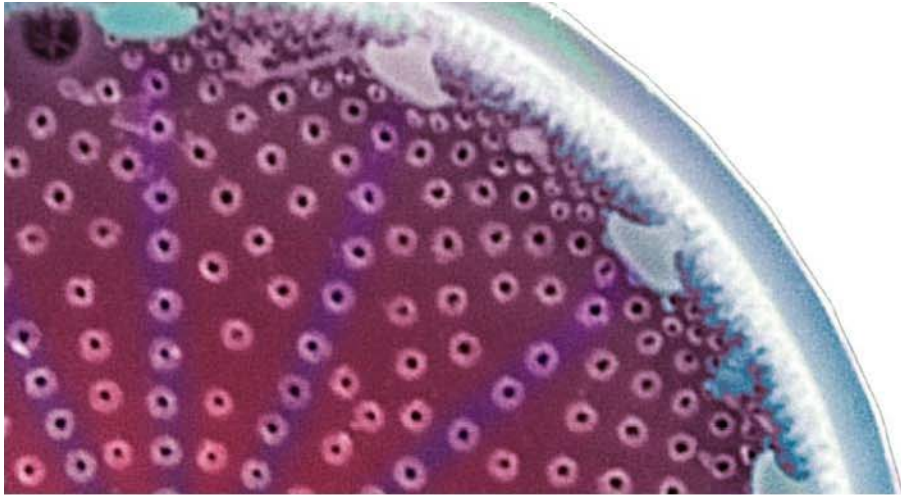
How We Develop Drugs

Traditional approach

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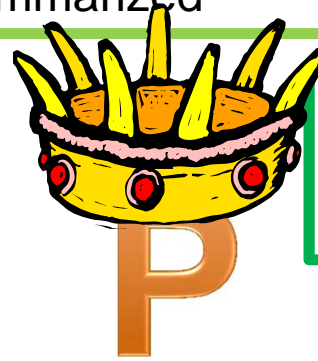*Navigating* the new health
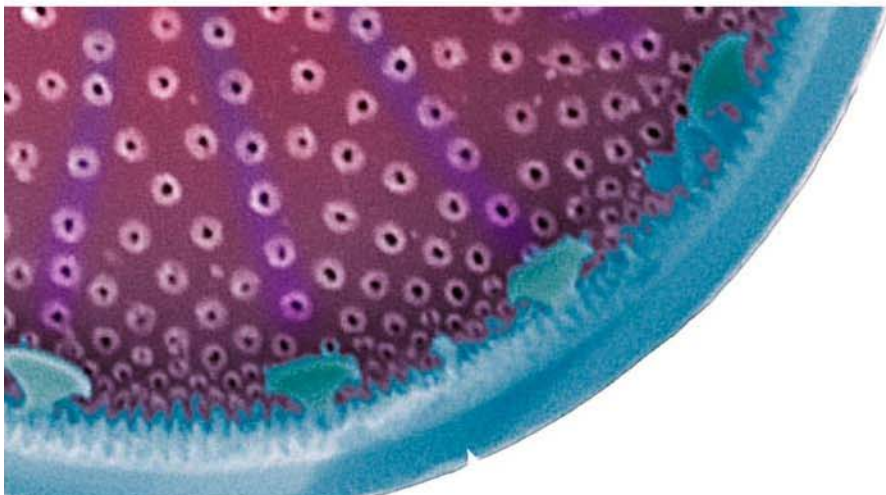
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Statistical Models by Phase

PK Models (NCA)
Safety look in small cohort

Analysis of Variance
        Lower power
Safety summarized

χ^2 test, CMH, t-test, or ANOVA
        High power
Safety summarized

Why isn't this good enough now?

– More financial pressure to succeed
  • Less resources (time, money, people) to work on trials
– More difficult to find novel drugs
– Standards have risen
  • tQT now required
  • Subpopulations
    – Pediatric
    – Renal or hepatic impairment
    – Safety is more of a concern
    – Regulatory requirements have gone up
      » 1996: > 50 NME approved by FDA, average cost $400 M
      » 2012: < 25 NME approved by FDA, average cost $2.5 B

Drugs Aren't Progressing

– Phase II failure rate increasing

- 2006: 72% failure rate
- 2008: 82% failure rate
  - 51% failed due to efficacy
  - 17% failed due to safety
  - 29% failed due to strategic reasons
- 2008: 18% progression

– Phase III failure rate increasing

- 2008: 50% failure rate
  - 66% failed due to efficacy
  - 21% failed due to safety

$400 M trial for Phase III

Business Model Not Sustainable

– Payors are pressing to hold down costs

– Development costs going up

– Time pressure to get drugs to market faster
  - First mover advantage
    – Studies have not shown it to be real, but management believes it
  - Operational focus
    – Aggressive FPI, LPO timelines
    – Protocol writing: Hurry up and wait

– In a nutshell
  - Simple analyses
  - Not much integration of data (e.g., efficacy and safety)
  - Dosing regimens chosen by medical leads based on intuition
  - Phase II's are practice for Phase III

Recap

– Traditional approach

- Simple statistical analyses without predictive ability
- Not much integration of data (e.g., efficacy and safety)
- Dosing regimens chosen by medical leads based on intuition and similarity to existing products
- Phase II's are practice for Phase III
- Silos among disciplines

MBDD Can Help

– Model-Based Drug Development
  - Using mathematical/statistical/computational models to represent biology and treatment practice
    – Includes PK, PD, dose-response
  - Analyses more complex
    – Nonlinear mixed-effect models (alias: population models)
  - Efficacy and safety data can be incorporated into a single, large model
  - Phase II's are *not* practice for Phase III, but are to gain knowledge
  - Integrate domain knowledge from several disciplines
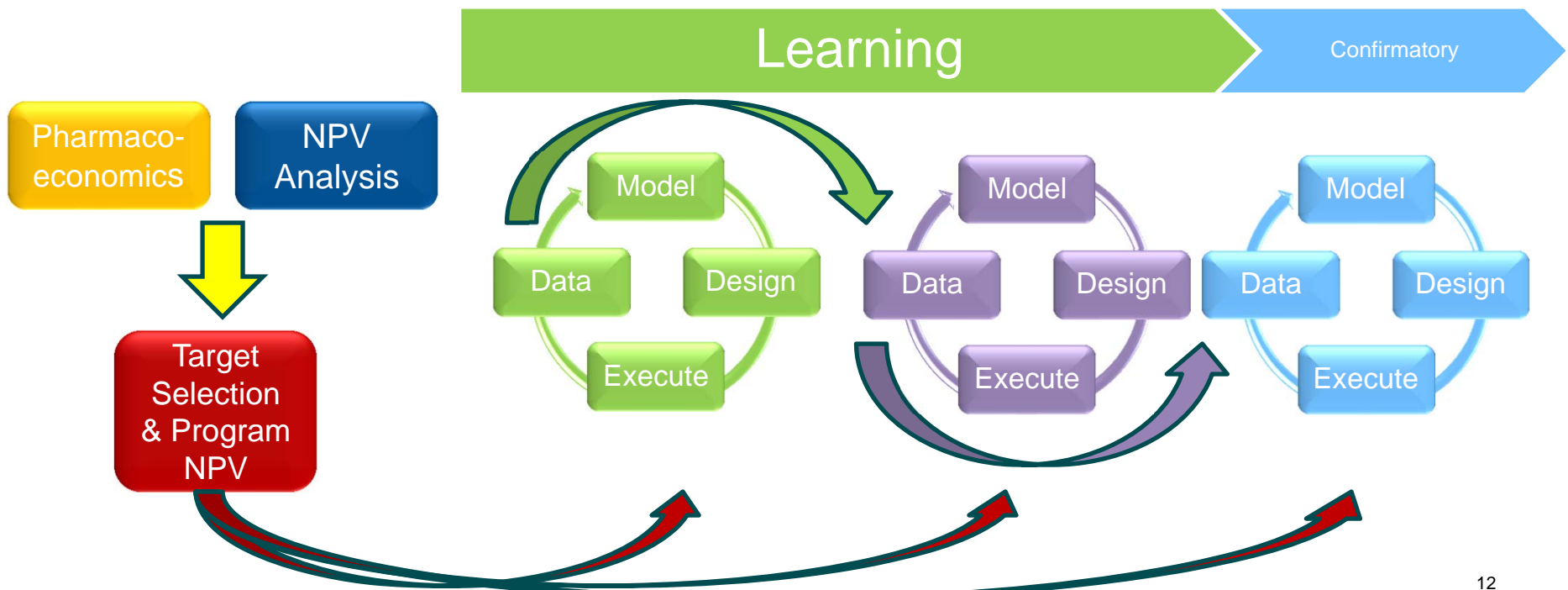
MBDD Across Phases
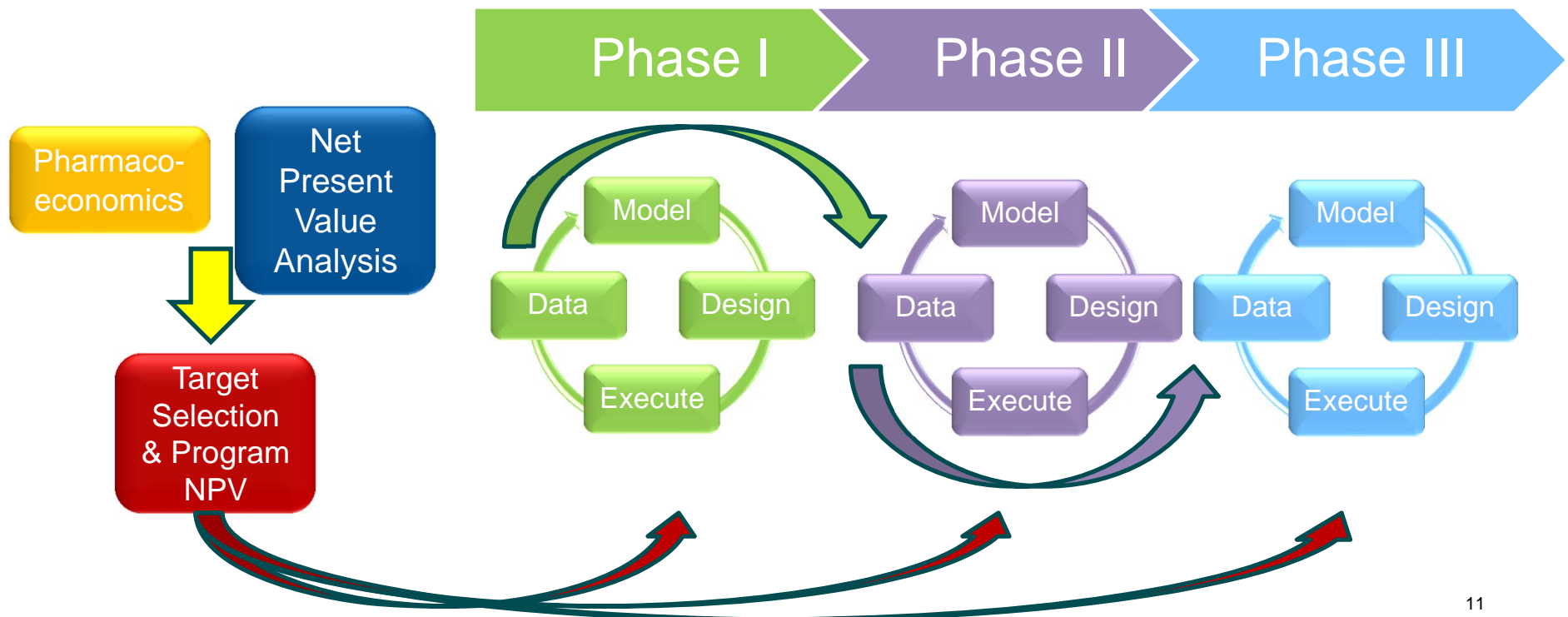
Phase I and II are learning phases
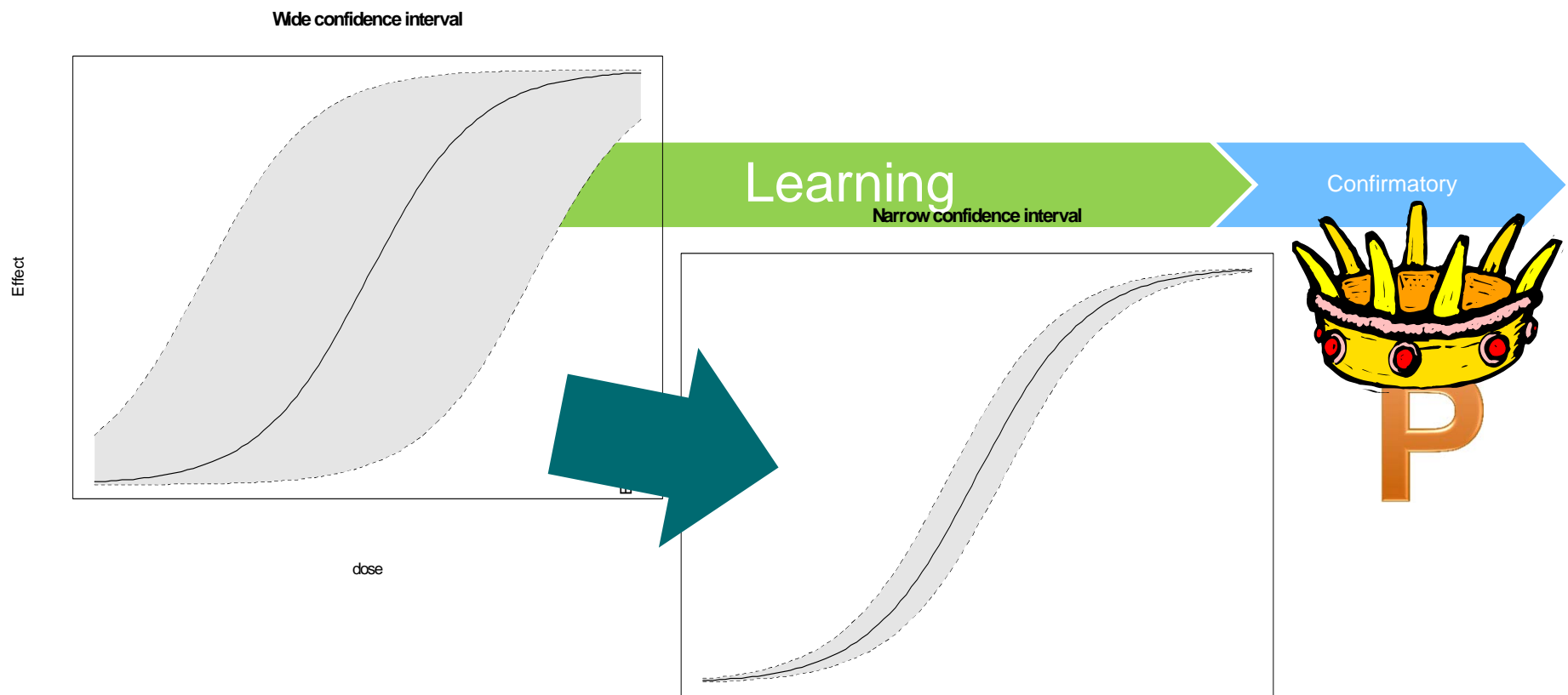
MBDD Across Phases

Phase I and II are learning phases, where knowledge of the drug effects improves over time.
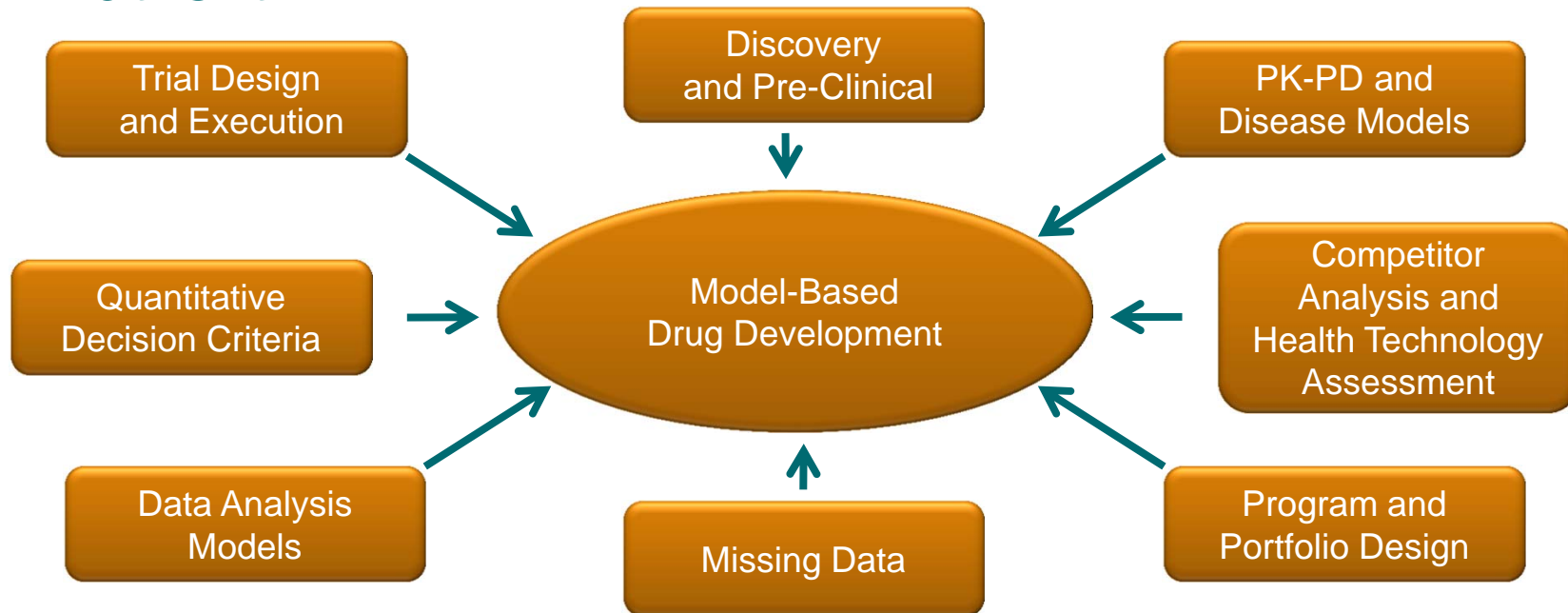
MBDD Across Phases

Phase I and II are learning phases, where knowledge of the drug effects improves over time.


Wide confidence interval

Effect

dose

Learning

Narrow confidence interval

Confirmatory

P

dose

Model-Based Drug Development: What Is It?

Trial Design and Execution → Model-Based Drug Development

Discovery and Pre-Clinical → Model-Based Drug Development

PK-PD and Disease Models → Model-Based Drug Development

Quantitative Decision Criteria → Model-Based Drug Development

Competitor Analysis and Health Technology Assessment → Model-Based Drug Development

Data Analysis Models → Model-Based Drug Development

Missing Data → Model-Based Drug Development

Program and Portfolio Design → Model-Based Drug Development

Derived from the RL Lalonde, et al. "Model-based Drug Development." Clinical Pharmacology & Therapeutics. Vol .82(1); pgs 21-32. July 2007.

MBDD is the development of integrated analyses (models) of available data (i.e., internal and external sources) and their application to inform strategy, trial design, and decision-making in drug development.

MBDD goal is to utilize internal and external data in a quantitative manner to improve drug development strategy and decision-making.
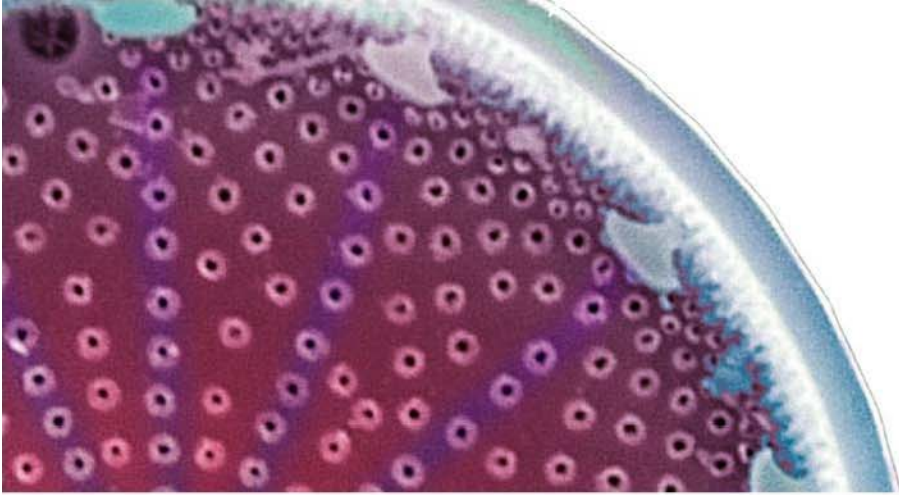
Examples of Models in MBDD
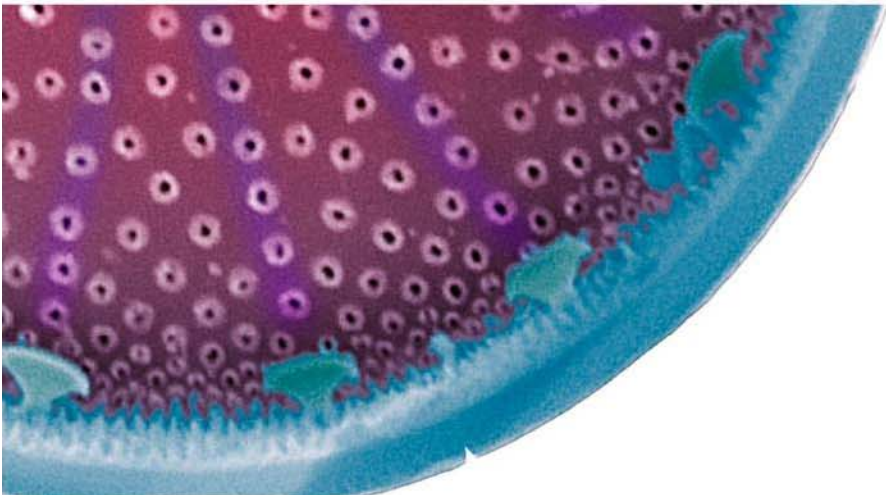
Randomized Concentration-Controlled Trial

- Mycophenolate mofetil was being developed for kidney transplant, but the drug was renally cleared

- Need to control blood concentrations to establish benefit

- Developed PK/PD model relating dose to AUC, and AUC to P(rejection)

RCCT

- P(Organ rejection) = $a + d/\{1 + \exp(-b[\log AUC - c])\}$
- AUC = $\gamma_1 + \gamma_2$ dose, $\gamma_1 \sim N(0, v^2)$

- Randomize to AUC levels
- Visit 1
  - Dose subject
  - Collect blood draws, get AUC
- Visit 2
  - Bayesian adjustment to dose
  - Dose subject
  - Collect blood draws, get AUC
- Visit n

RCCT

– Simulated trial parameters

- Sample size

- Dose adjustment limits

- Effect of maximum dose

- Analysis methodology for test H_0: Flat curve

– Other results from simulation as well

- Number of tablets of various sizes

– Successful trial

Case Study 1:
Program Simulation

- Several options for design Phase IIa and Phase IIb

- For simplicity, we will focus on sample size and doses here

- Objective was to pick doses to carry into Phase III that maximized the probability of success (P<0.05 in Phase III)

- Sample size was constrained to be 1000 in Phase IIb and 1000 in Phase III

Case Study 1:
Strategy #1: Original Plan

Phase IIa

Phase IIb

Phase III

Active dose

1   2   3   4

12   12   12   12

6   6   6   6

Placebo

Active

500 subjects

500 subjects

Placebo

Active

500 subjects

500 subjects

Placebo
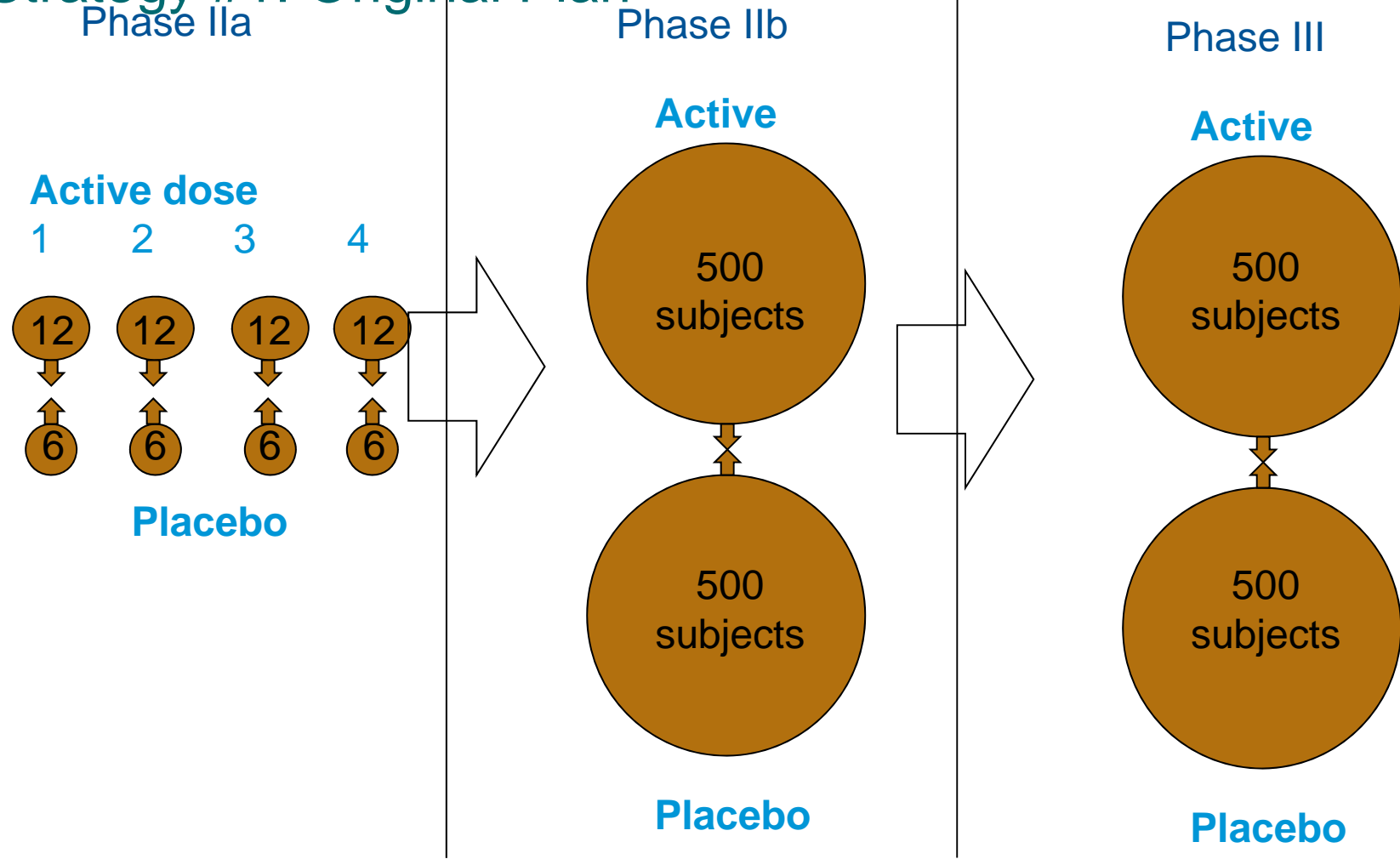
Case Study 1:
Strategy #2: Use Many Doses In IIb
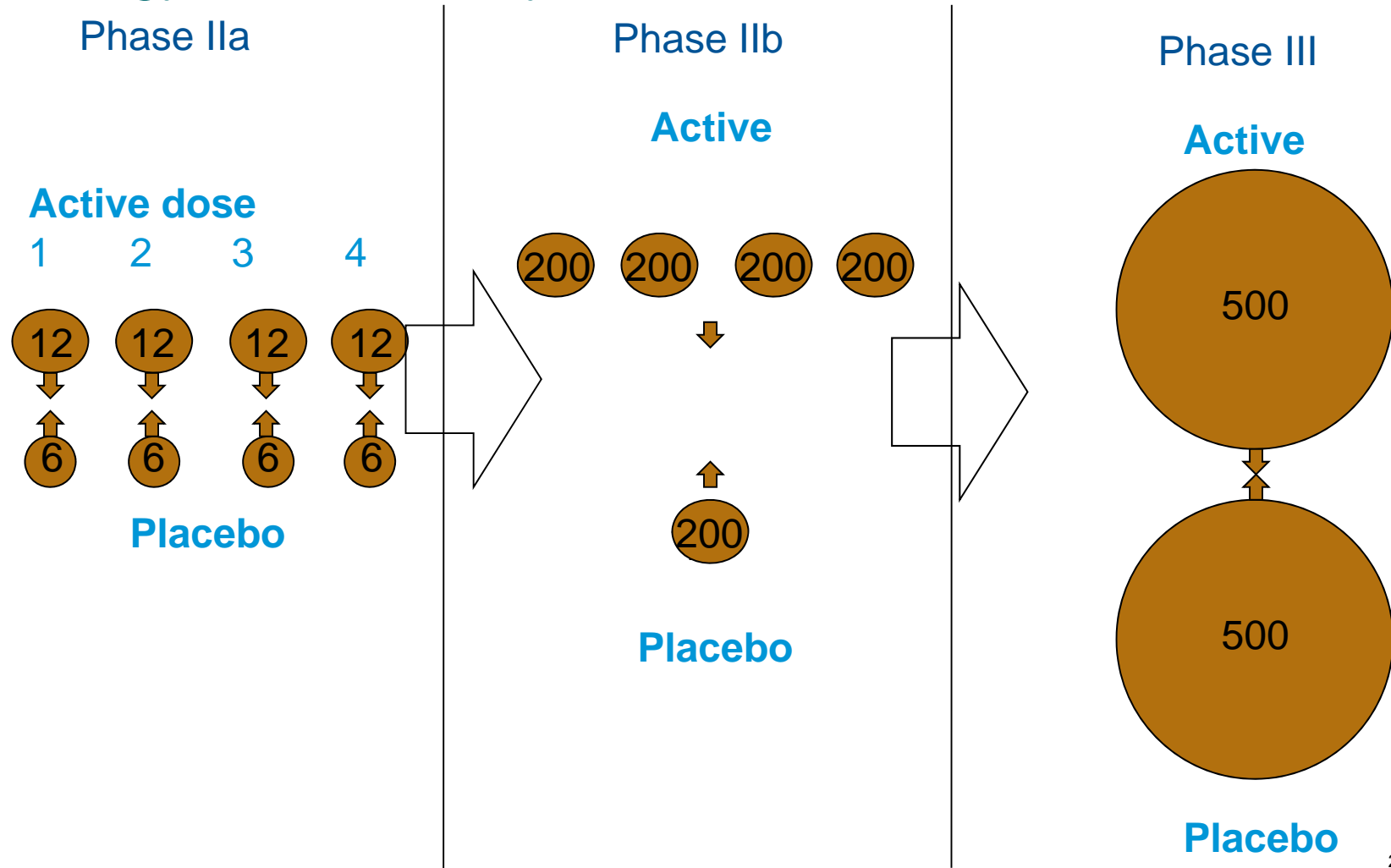
Case Study 1:
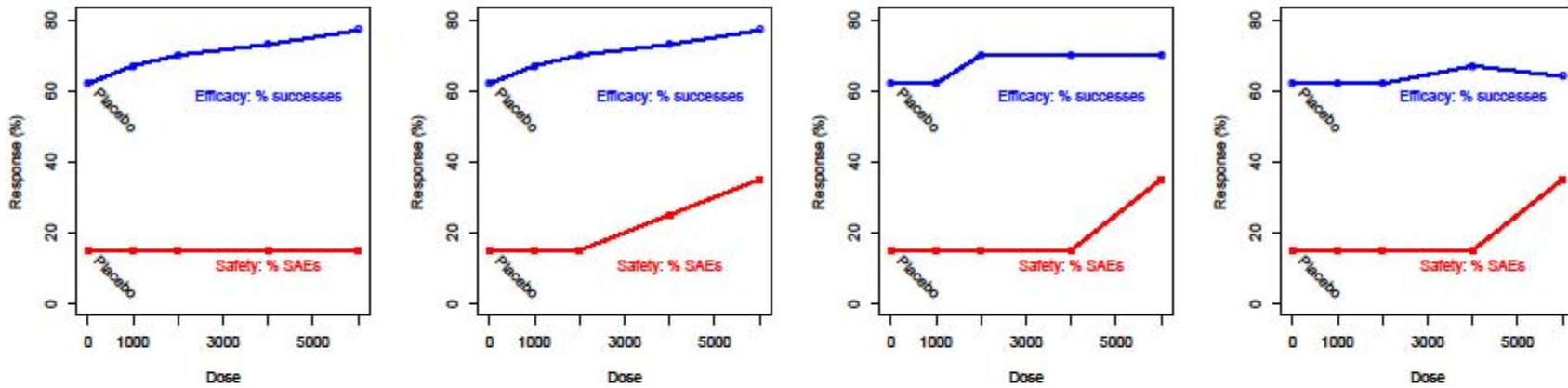# Strategy #3: Use Two Safe Doses From IIa

Phase IIa

Phase IIb

Phase III

Active dose

1   2   3   4

Active

Active

12   12   12   12

333   333
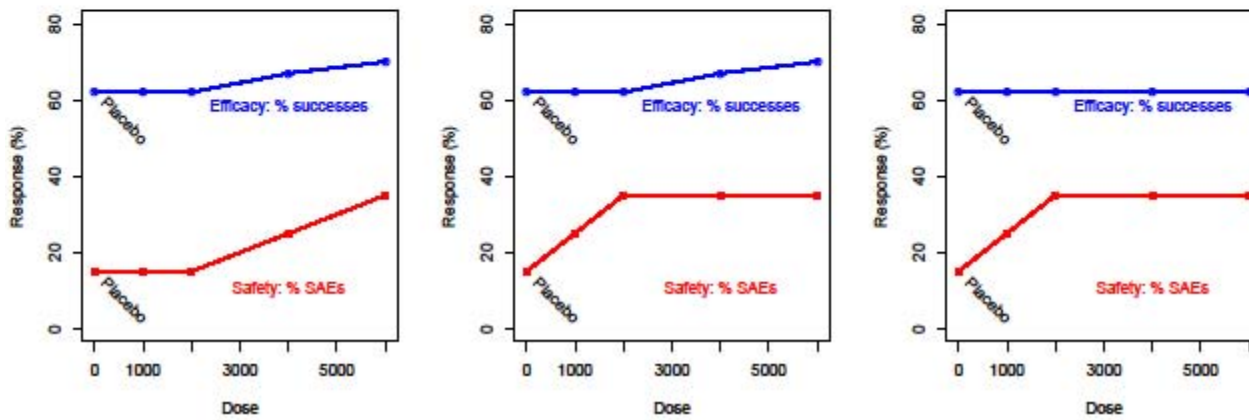
500

6   6   6   6

Placebo

333

500

Placebo

Placebo
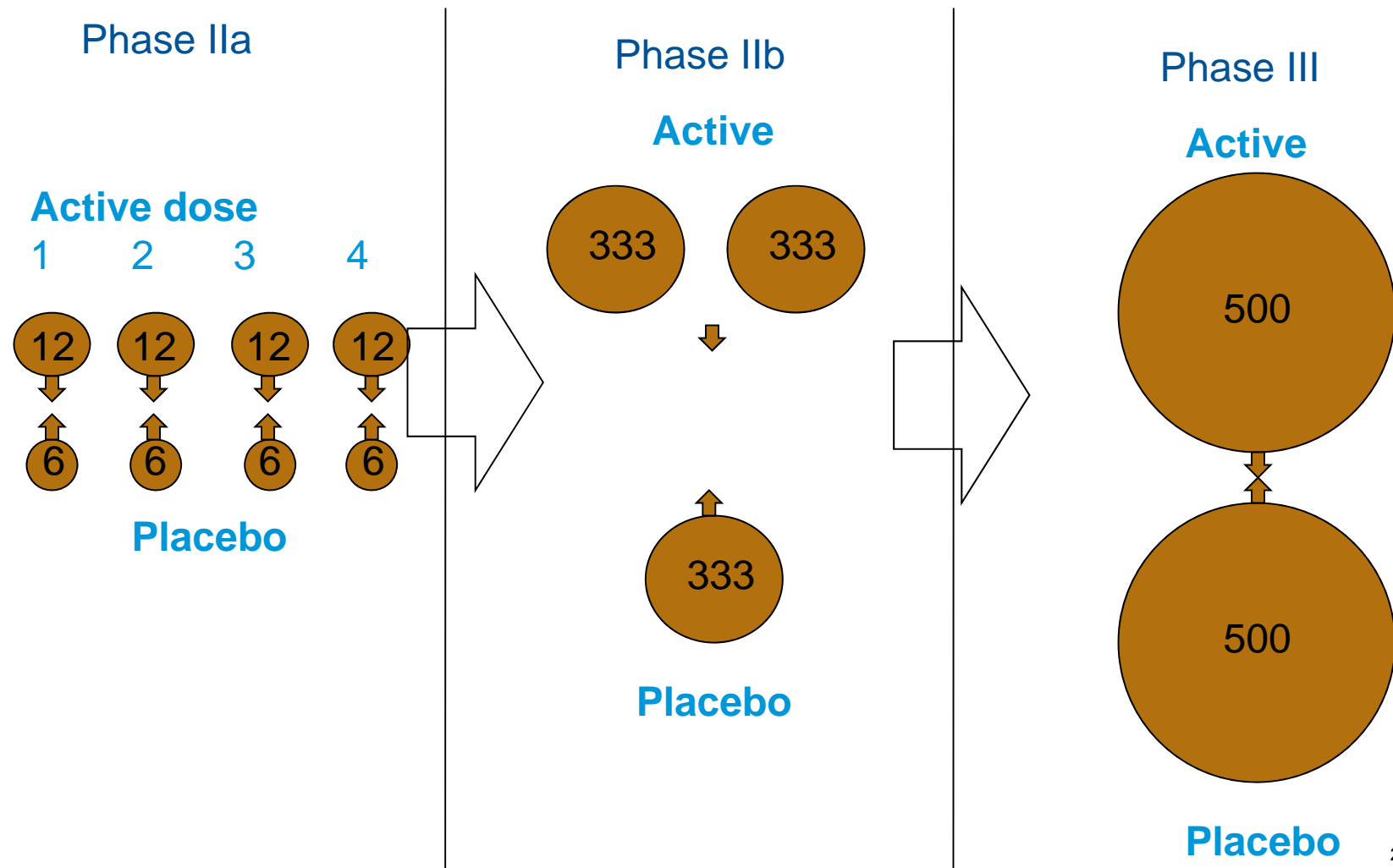
Case Study 1: Scenario Analyses
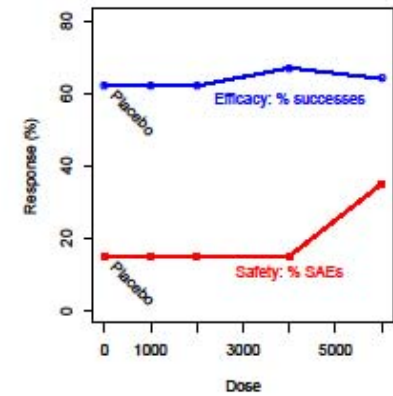
Scenarios to cover best cases…
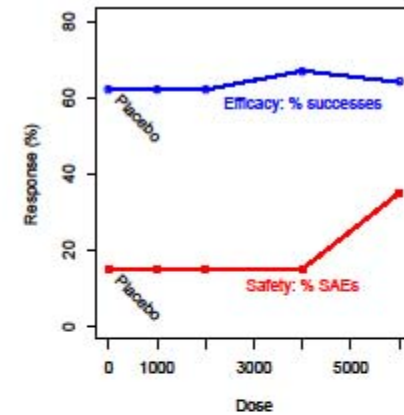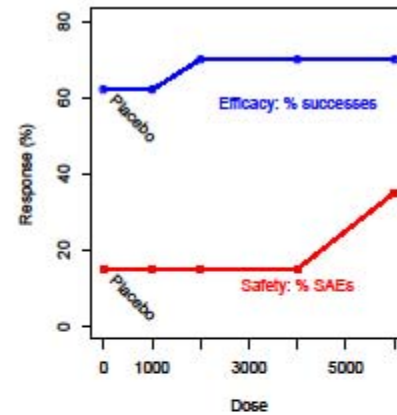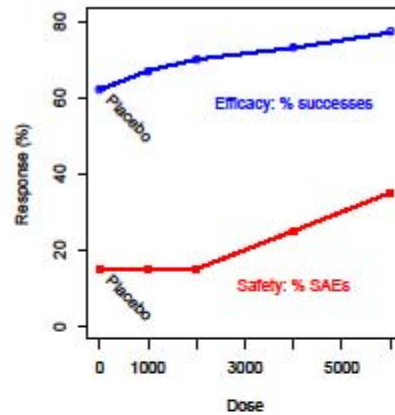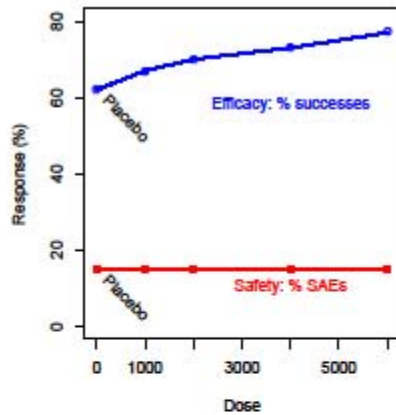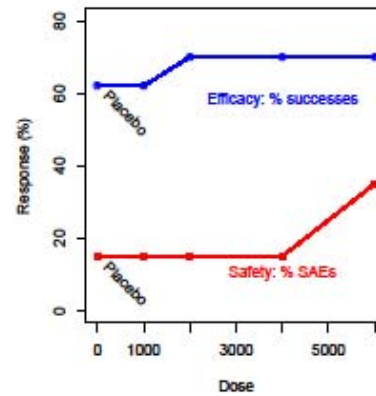
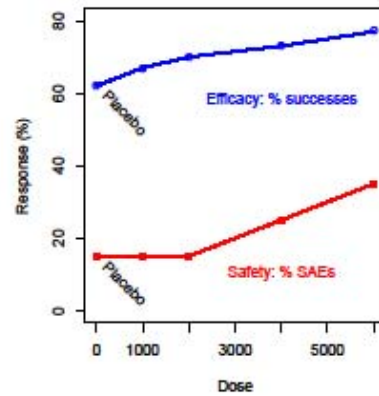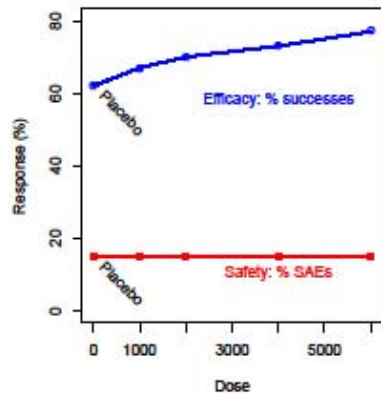# Case Study 1: Scenario Analyses

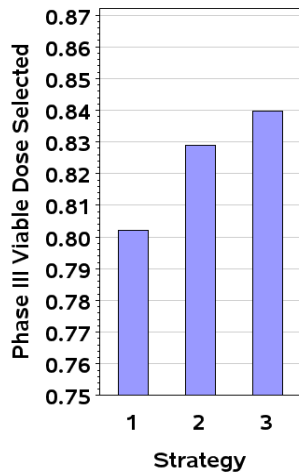Scenarios to cover best cases…

… through to worst cases

Case Study 1: Scenario Analysis Results – Phase III Success

Scenarios with viable doses
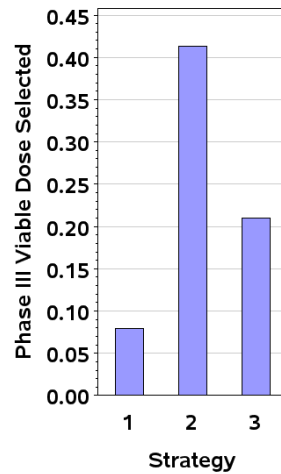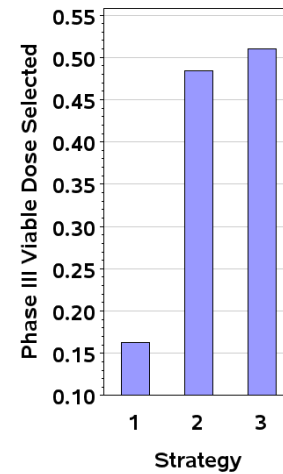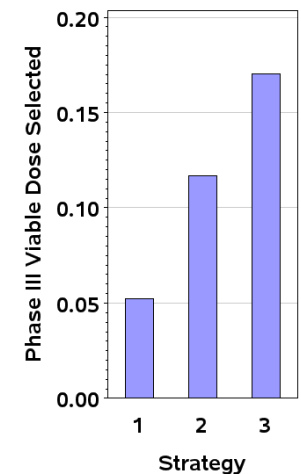
Case Study 1: Scenario Analyses Results – Stopping In IIb
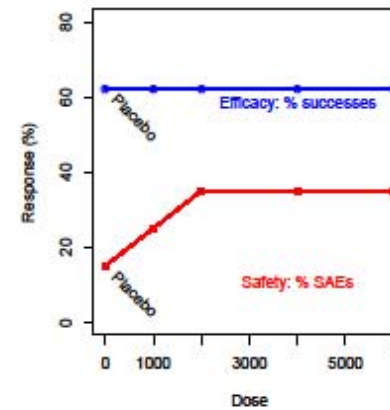
Scenarios with no viable doses
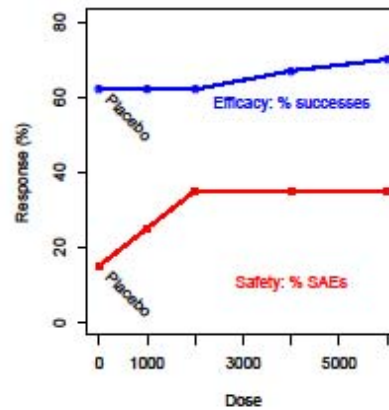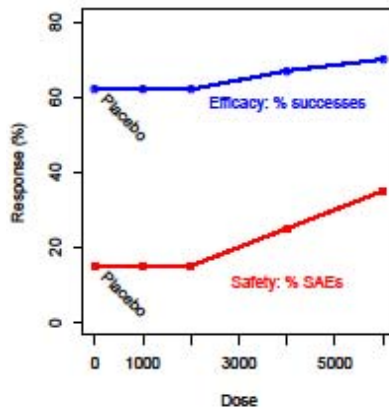
Scenario 5
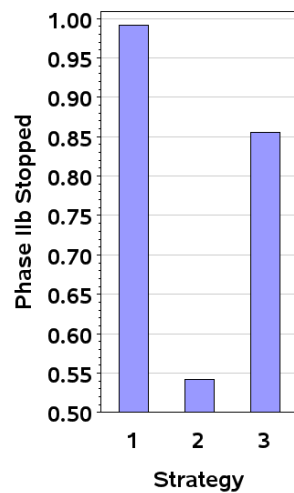
Scenario 6
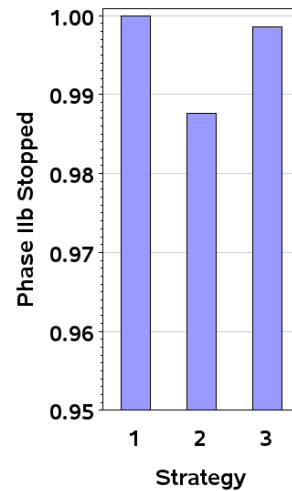
Scenario 7
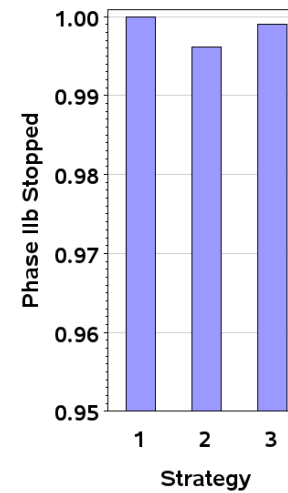
Case Study 1: Summary

– Seven safety+efficacy scenarios simulated to assess risks and benefits

– 3 strategies assessed, fourth ongoing

– Simulations are focussed on giving the multifunctional development team what it needs

  • e.g. Idea for strategy #3 came as a result of team discussions of simulations of strategies #1 and #2

– Simulations facilitate development team in thinking productively about new strategies

Case Study 2: Modeling Study Startup Methods for Cycle Time Distribution Estimation

Time to Site Start Up: Distribution

Based on Recent Historical Data
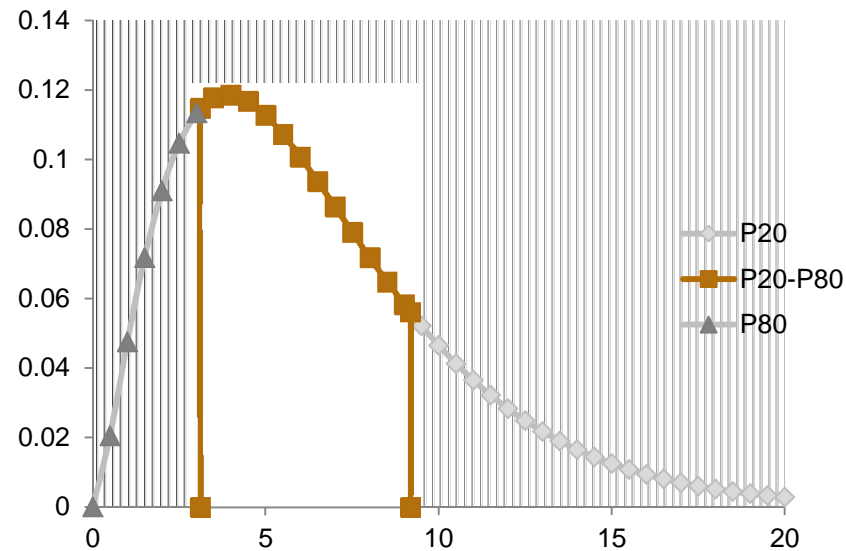
Leverages Quintiles Historical Data

Case Study 2:
Study Startup Simulation of Process
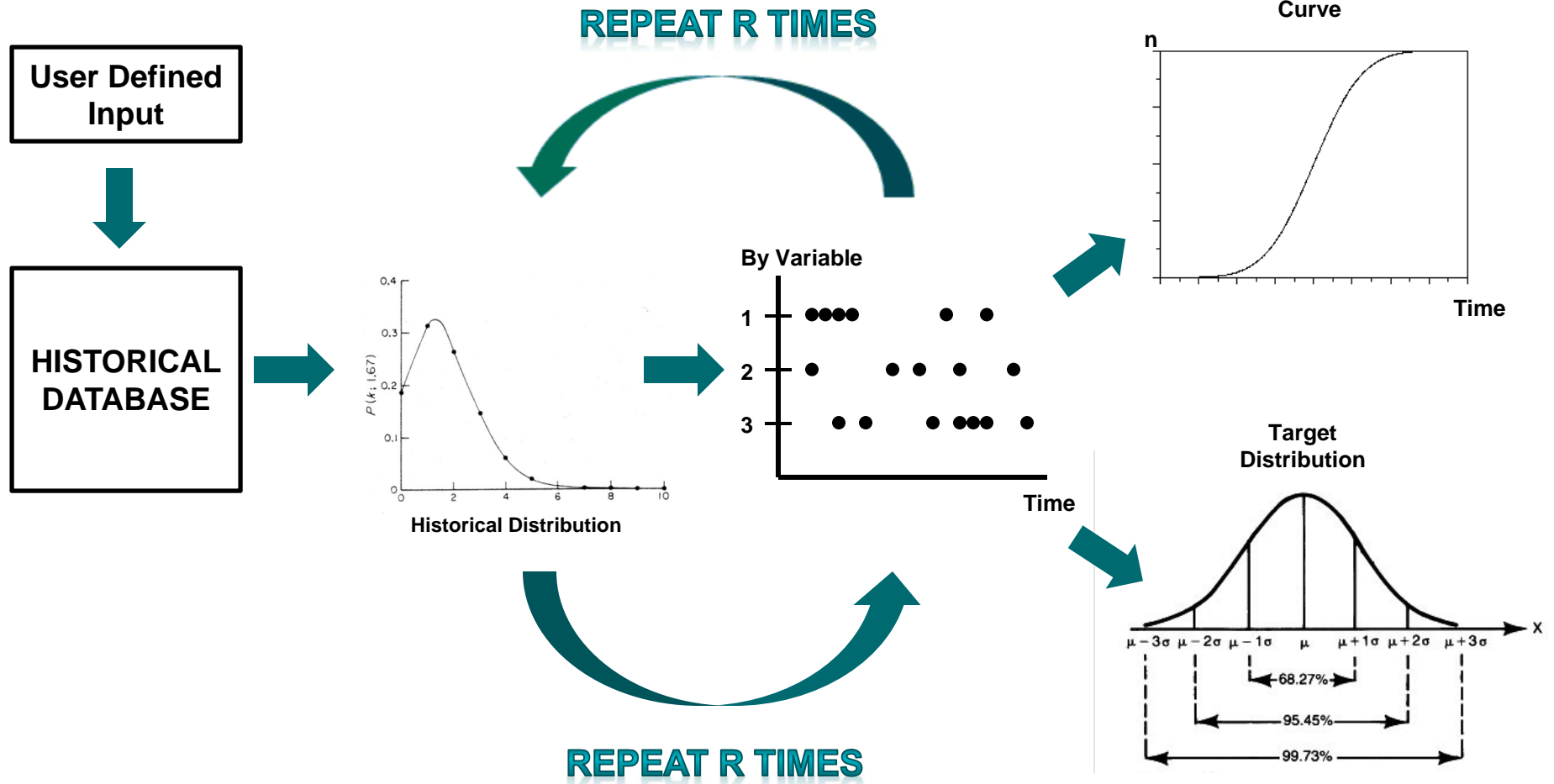
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User Defined Input

HISTORICAL DATABASE

Historical Distribution

$P(k;1.67)$

By Variable

1

2

3

Time

Cumulative Curve

n

Time

Target Distribution

$\mu-3\sigma$ $\mu-2\sigma$ $\mu-1\sigma$ μ $\mu+1\sigma$ $\mu+2\sigma$ $\mu+3\sigma$ X

68.27%

95.45%

99.73%

REPEAT R TIMES

Case Study 2:
Study Startup Simulation of Process

– Country differences

  • Use to optimize distribution of patients among countries

– Adjust based on trial data

  • Can increase sites, plan additional or scale back recruitment, based on predictions from current data combined with historical performance

– Reduced time to LPLV substantially

Case Study 2: Example Results

Case Study 2:
Study Startup Simulation of Process

– Country differences

- Use to optimize distribution of patients

– Adjust based on trial data

- Can increase sites, plan additional or scale back recruitment, based on predictions from current data combined with historical performance
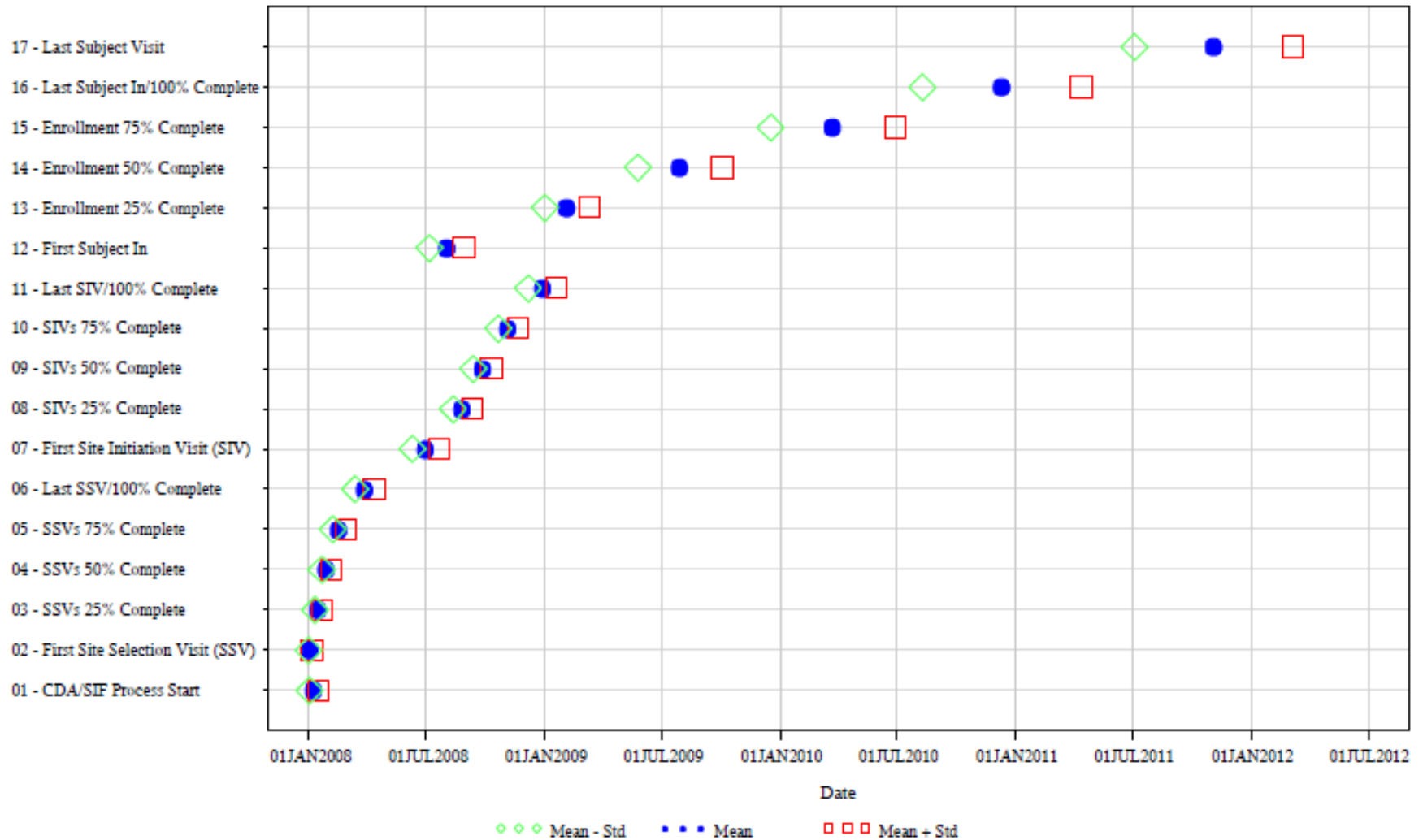
– Reduced time to LPLV substantially

Case Study 3:
Biomarker Modeling

- **Population:** Patients Infected with a Specific Type of Virus

- **Treatment:** New Molecular Entity (NME)

- **Problem:** Multiple Biomarkers Related to Efficacy of NME; Which Ones Predict Best?

  What's the Dose-Response Curve Look Like?

  Should We Screen the Biomarkers to Enhance the Power of the Study, or is it Quicker to Include All-Comers?

- **Methodology:** Model Fitting to Find Biomarkers

  Dose-Response Modeling to Fit the Curves

  Trial Simulation (Clinical and Operational) to Answer Questions of Inclusion / Exclusion Criteria

Case Study 3:
Biomarker Modeling

Change log Viral Load vs Day 15 Ctrough
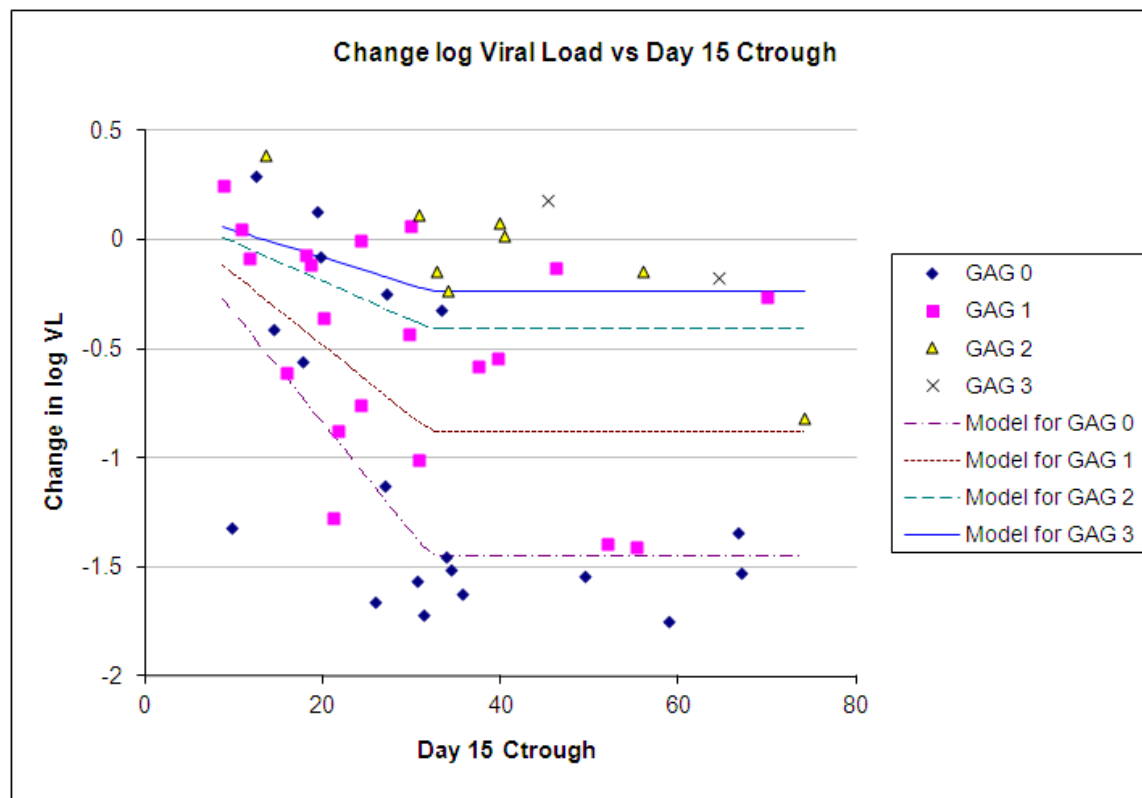
– **Results**

- Found 5 biomarkers predictive of patients most likely to respond to therapy

- Response is function of number of biomarkers present

- Dose-response curve was evident (statistically significant)

- Depending on recruitment rate, could use biomarkers to enhance the probability of success in trial design

Case Study 3:
Impact

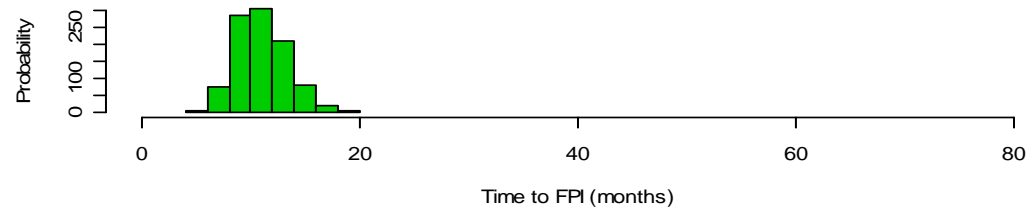- Targeting concentration of 30 (have PK model as well)

- Inclusion

  - All Comers (N=82 for 80% power)

  - Best 2 inclusion groups (N = 22)

  - Best 1 inclusion group (N = 16)

- What is the preferred I/E criteria?

  - Will approach through simulation

  - Other variables could be included, including differential drop out rates, etc.

Case Study 3:
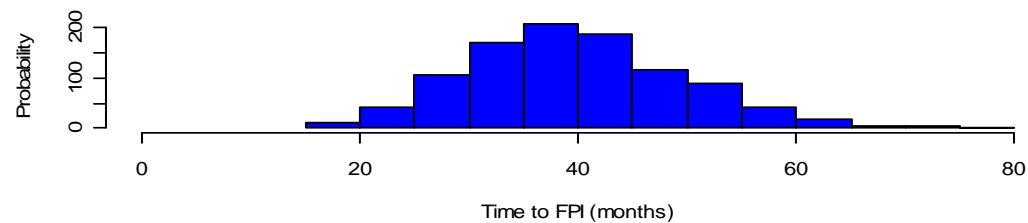# Biomarker Modeling: Options for planned studies
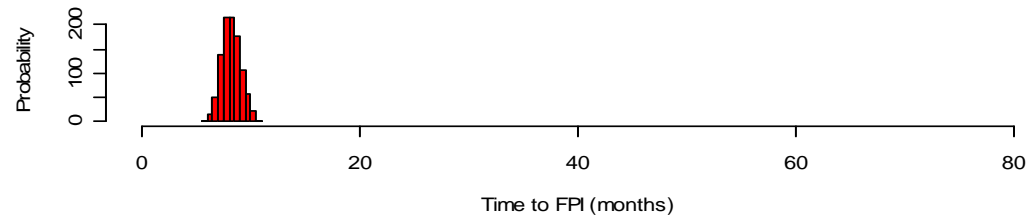
Case Study 4:
Disease Progression Modeling & Simulation

- **Problem:**   Need to Design Studies in Rheumatoid Arthritis (RA)

- **Constraints:** Rarely Enough Data to Support One-Off Modeling

       Preferred Endpoints Not Consistent Between
       US and EU

- **Methodology:** Construct Dose- and Time-Response Models in RA for
       Several Different Endpoints

       Model Constructed in Pharsight's Trial Simulator
       for Quick Deployment to Design Trials

       Developing Models for etanercept, adalimumab,
       tocilizumab, anakinra, CZP, golimumab, infliximab,
       abatacept

       Development Used for Comparators in Simulations and
       Experience with Similar Compounds Applied to a Novel
       Compound

Case Study 4:
Disease Progression Modeling & Simulation

Tocilizumab:
red-MTX, green-Toci 8mg/MTX, blue-Toci 4mg/MTX
hollow triangle-Pred, filled circle-Actual
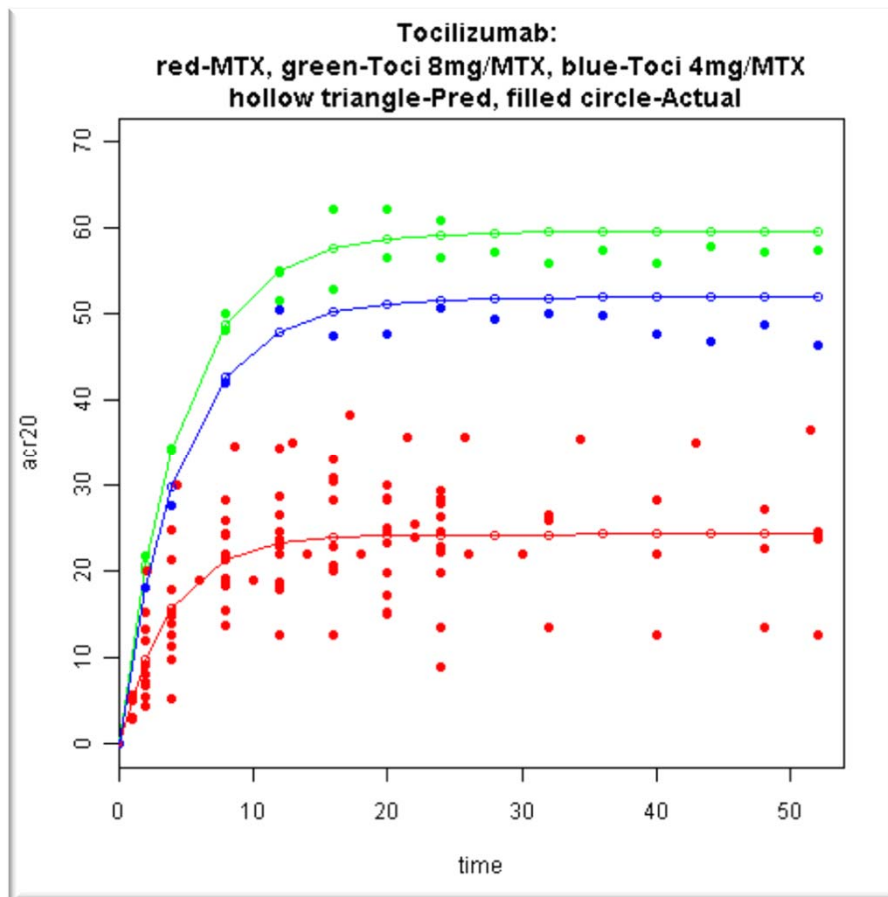

– **Client Uses**

- Tocilizumab Example
    - Model for other compounds also

- Model Incorporated into Several Trial Simulations

- Plan Biosimilar Program

- Utilize Adaptive Design
    - PK BE
    - Followed by Sample Size Re-estimation

- Apply Design Changes When Changing Endpoints (ACR20 to DAS28)

Case Study 4:
Disease Progression Modeling & Simulation
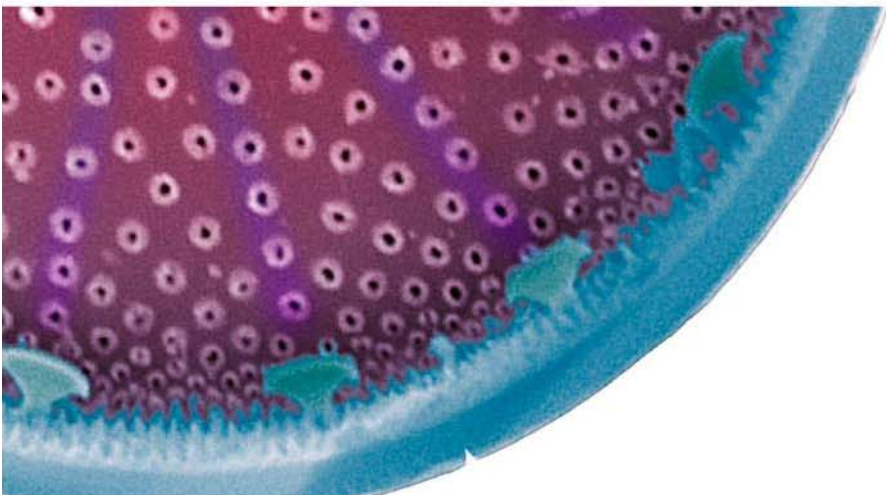
Drug/Dose Effects
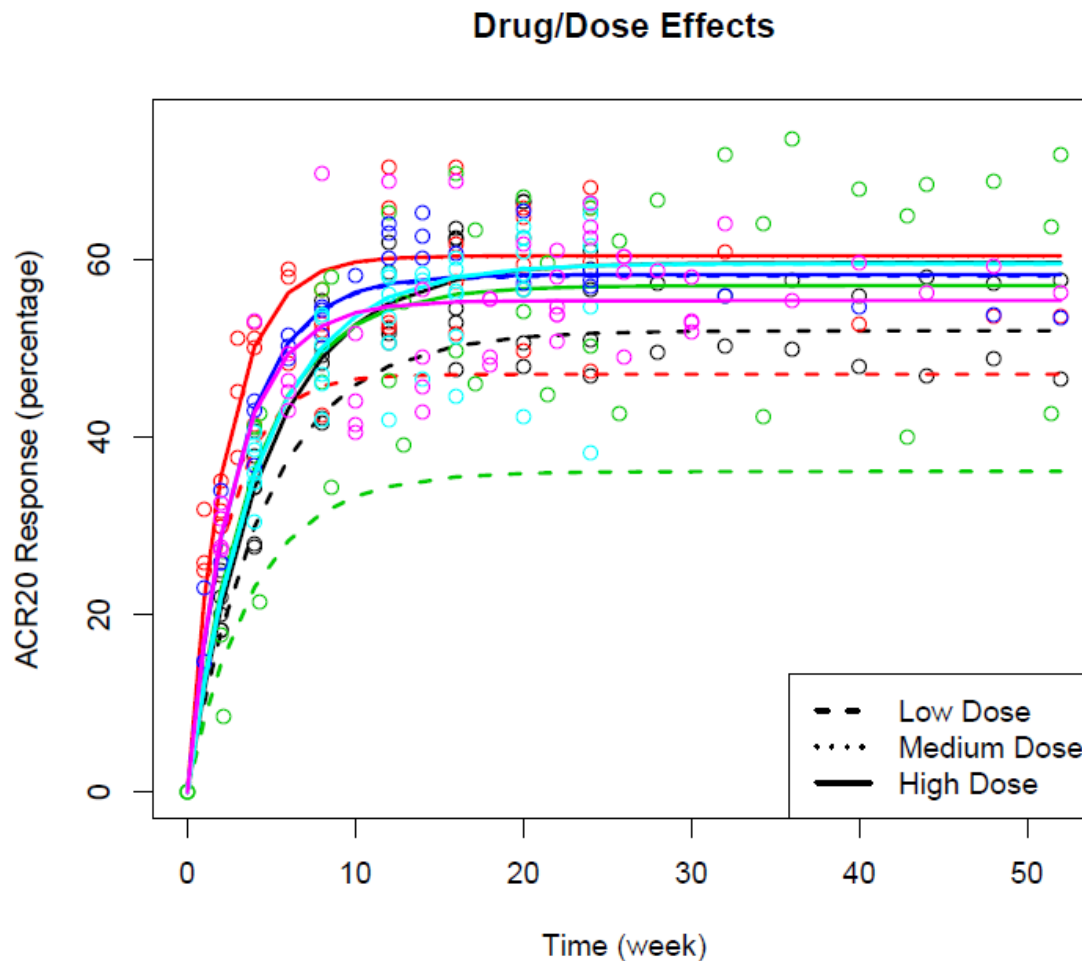
Case Study 4:
Impact

- Models used to design biosimilar trials

- Used as inputs into trial simulations

  - Design then optimized for length of trial, number of subjects, statistical analysis method, missing data handling, etc.

- Reduced proposed sample sizes
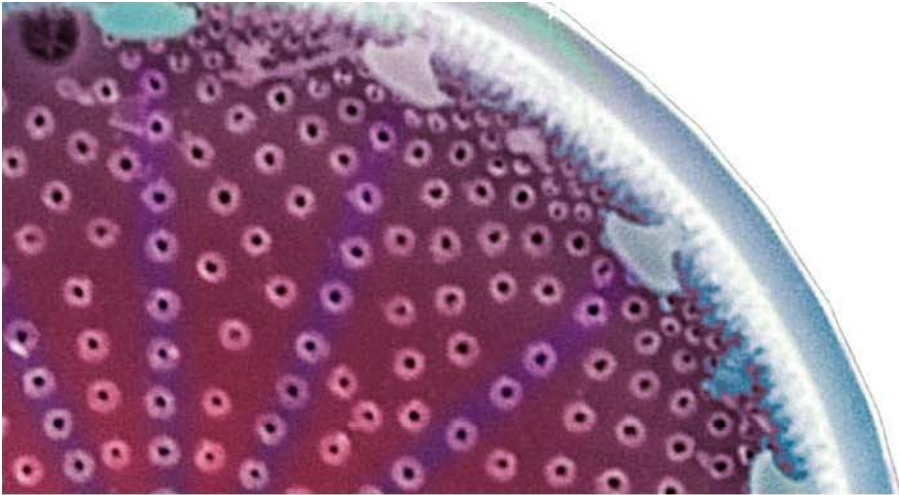
Success and Failure

Lessons Learned

Rheumatoid Arthritis

Media > Media Releases

Media Release

Roche

Basel, 2 March 2012

Roche's RoACTEMRA monotherapy showed superior improvement in rheumatoid arthritis signs and symptoms versus adalimumab monotherapy

Statistically significant greater improvement in signs and symptoms, as measured by mean change in DAS28 (primary endpoint), DAS28 remission and low disease activity, ACR20, 50 and 70 (secondary endpoints)

Recall Case Study 4:
Focus on just adalimumab and tocilizumab

Drug/Dose Effects
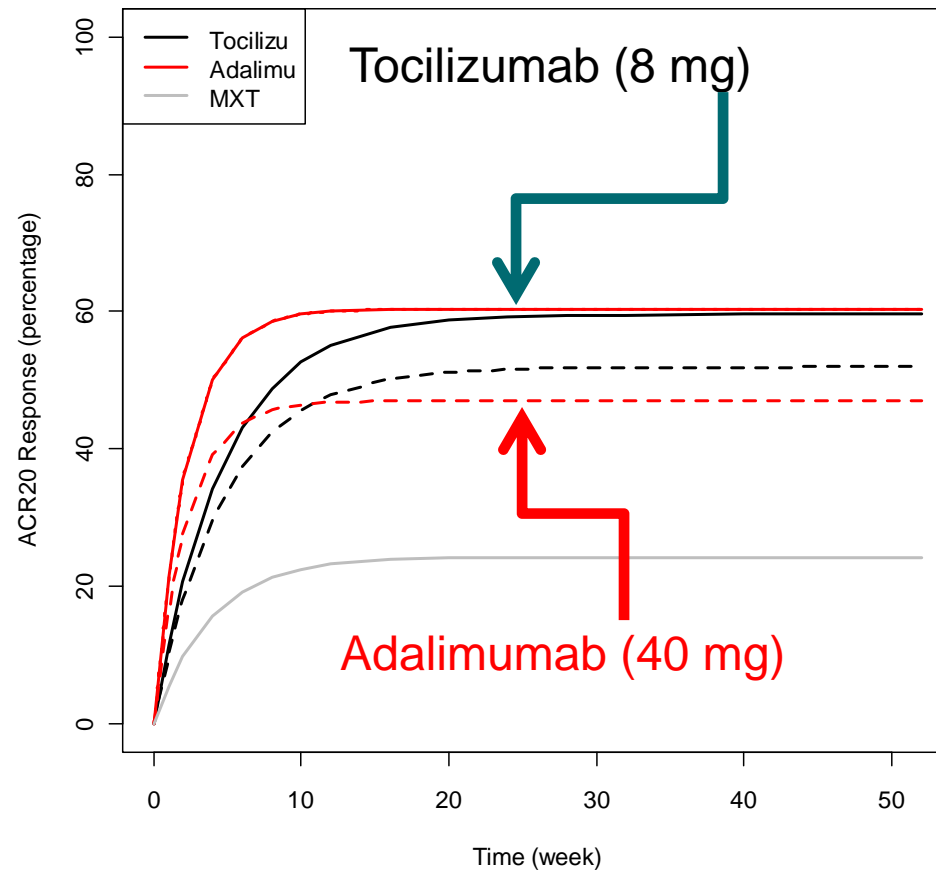
Our model uses methotrexate as background versus monotherapy in the Roche study, but we still predicted the results

Biologic PK/PD Model (betaseron)

- Used to treat multiple sclerosis

- Broad dose-response curve

- Never could develop a model to predict behavior beyond ANOVA model

Approval of gabapentin

– Gabapentin

- Originally approved for partial seizures of epilepsy in 1993
- Sponsor was seeking approval for post herpetic neuralgia
- Two trials conducted
  - Trial 1: placebo, 3600 mg/day
  - Trial 2: placebo, 1800 mg/day, 2400 mg/day

Food & Drug Administratino Modernization Act1997 (10,11), states in Section 115: " *. . . based on relevant science, that data from one adequate and well controlled clinical investigation and confirmatory evidence (obtained prior to or after such investigation) are sufficient to establish effectiveness."*

Source: Miller et al (2005)

Approval of gabapentin
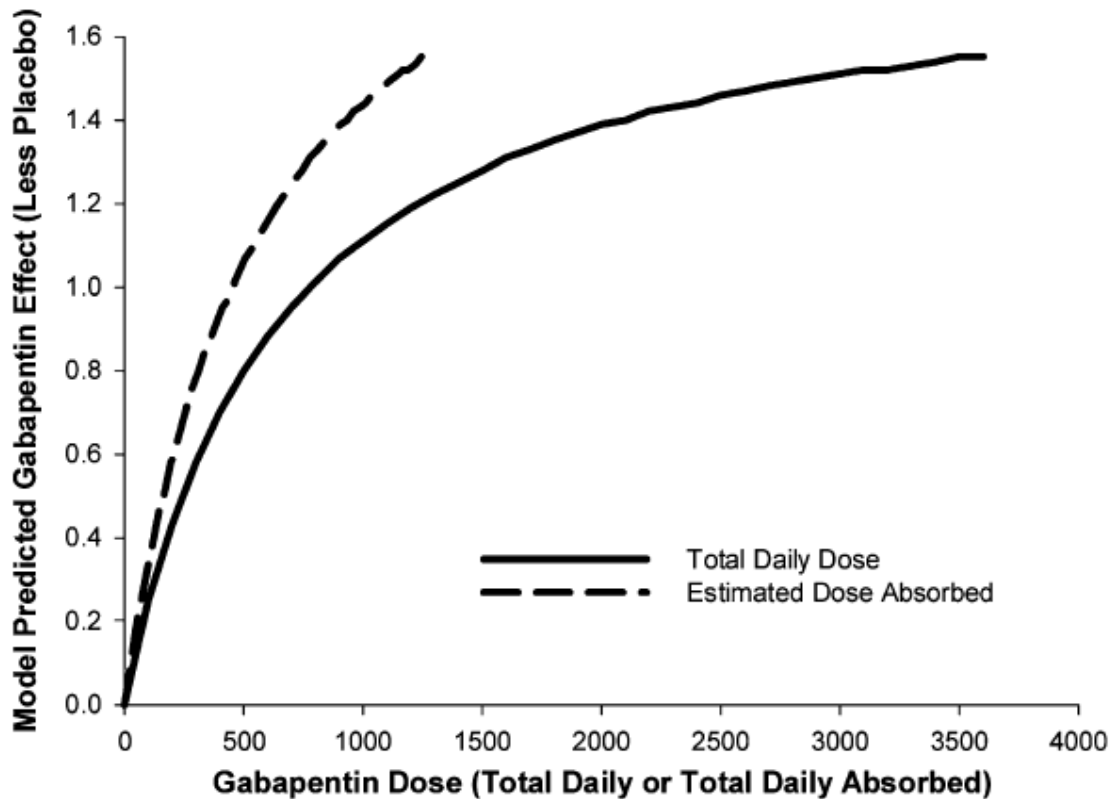
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Trial 1

Trial 2

Source: Miller et al (2005)

Approval of gabapentin

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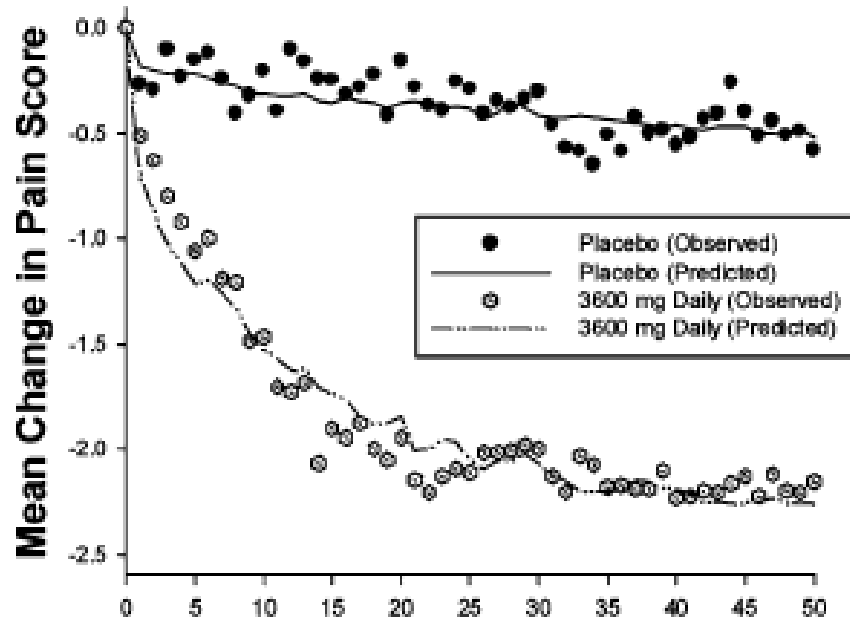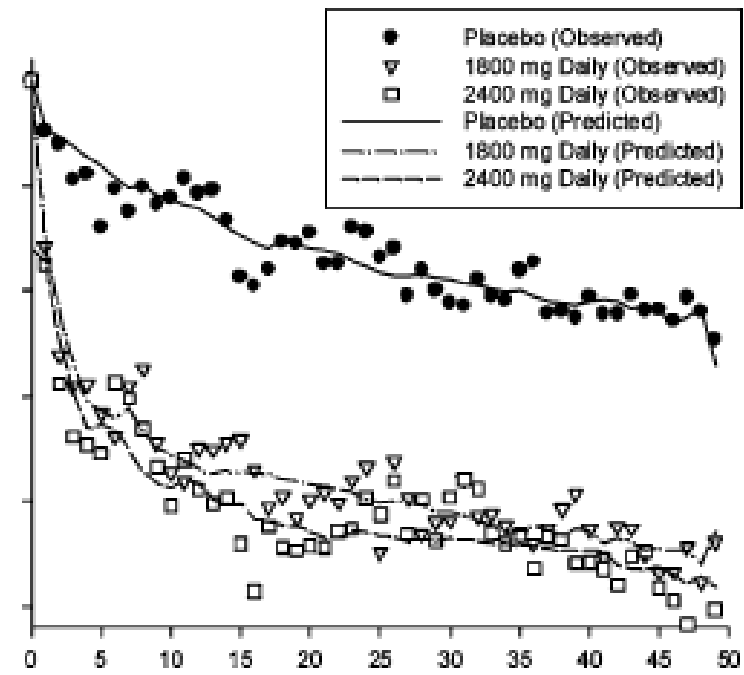
Source: Miller et al (2005)

- Result
  - Additional confirmatory trial not needed
    - Modeling provided the additional evidence needed for approval
  - Drug approved for this indication

Lessons Learned

- Models can predict clinical trial results
  - Need to spend effort to develop the models
  - Model becomes increasingly useful as it is being built
- For some compounds, not useful
  - Chiefly those with very broad dose-response curves, or binary effects
- Haste makes waste
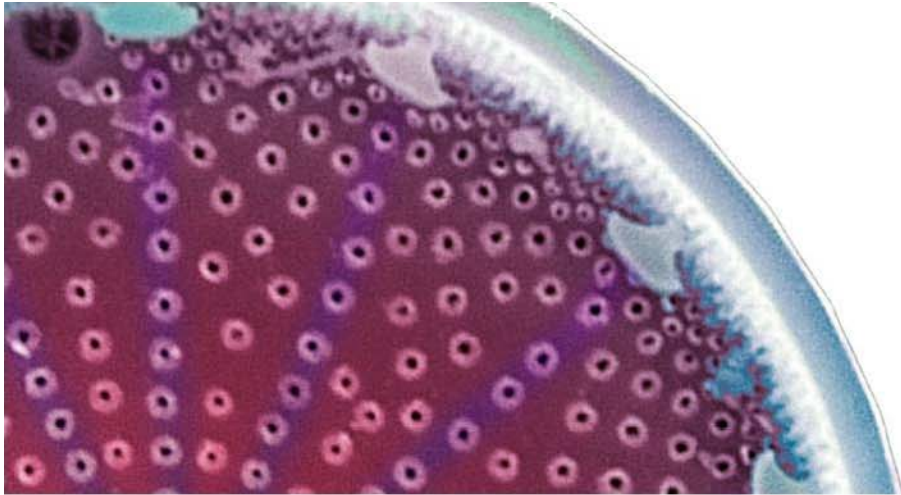
Organizational Issues and Benefits

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Navigating the new health

clinical | commercial | consulting | capital

Expectations need to be properly set
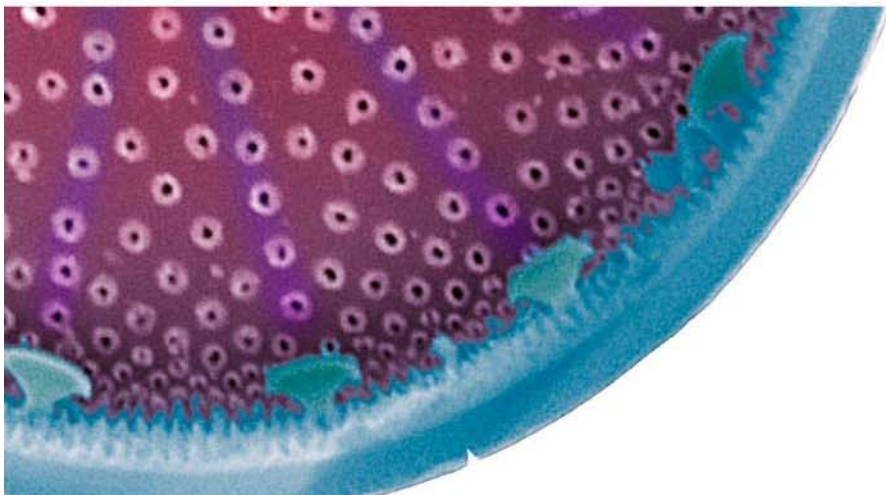
- MBDD and adaptive trials are not faster for an individual trial
- MBDD and adaptive trials are:
  - Faster for the program
    - Bridging based on models to avoid trials
    - Better identification of "good" doses
  - Increase chances of success
- Need access to people trained in the methodology
  - Technical skills: Statisticians, kineticists, pharmacologists, clinicians
  - Organization: Project managers, senior executives
  - Affected: Monitors, data managers, outsourcing executives, regulatory

Model Based Drug Development: The Return on Investment

QUINTILES

– Dr. Richard Lalonde (Head of Clinical Pharmacology, Pfizer) at American Conference on Pharmacometrics, 2008

- "Enhanced Clinical Trial Design (ECTD) initiative reduced the cost of our Phase 2 and 3 trials"

  – **SAVINGS of $75M in 2006 and $100M in 2007**
  – Joint Effort of Clinical Team and Pharmacometrics Group
  – Most Savings: Smaller Dose-Response Studies
    $\rightarrow$ Based on Dose-Response Models vs Pair-Wise Comparisons
  – Interim Analyses to Stopping Trials Early for Futility.
  – Time Savings to Conduct Studies with Fewer Patients

- Overall Metric:

$$\frac{\text{All Phase 2/3 Trials Clinical Cost}}{\text{Number of Successful Phase 3 Trials (Aggregated Over 3 Years)}}$$

Benefits

– Improves communication across disciplines

– Helps define what we know and how certain that knowledge is

– Can utilize many data domains to improve drug development

– Better decision making

Conclusions

– When properly implemented, MBDD and adaptive trials:

- Speed up development

- Improve decision making

- Improve probability of success

  – Kill assets that need to be killed

  – Develop assets fully that should be fully developed

– Benefits accrue most when used across whole development

– Already used for label claims

– Has proven use in reducing the number of trials in drug development (e.g., Miller et al 2008)