Impact of PK/PD, Disease Models and Personalized Medicine to Influence FDA Decisions

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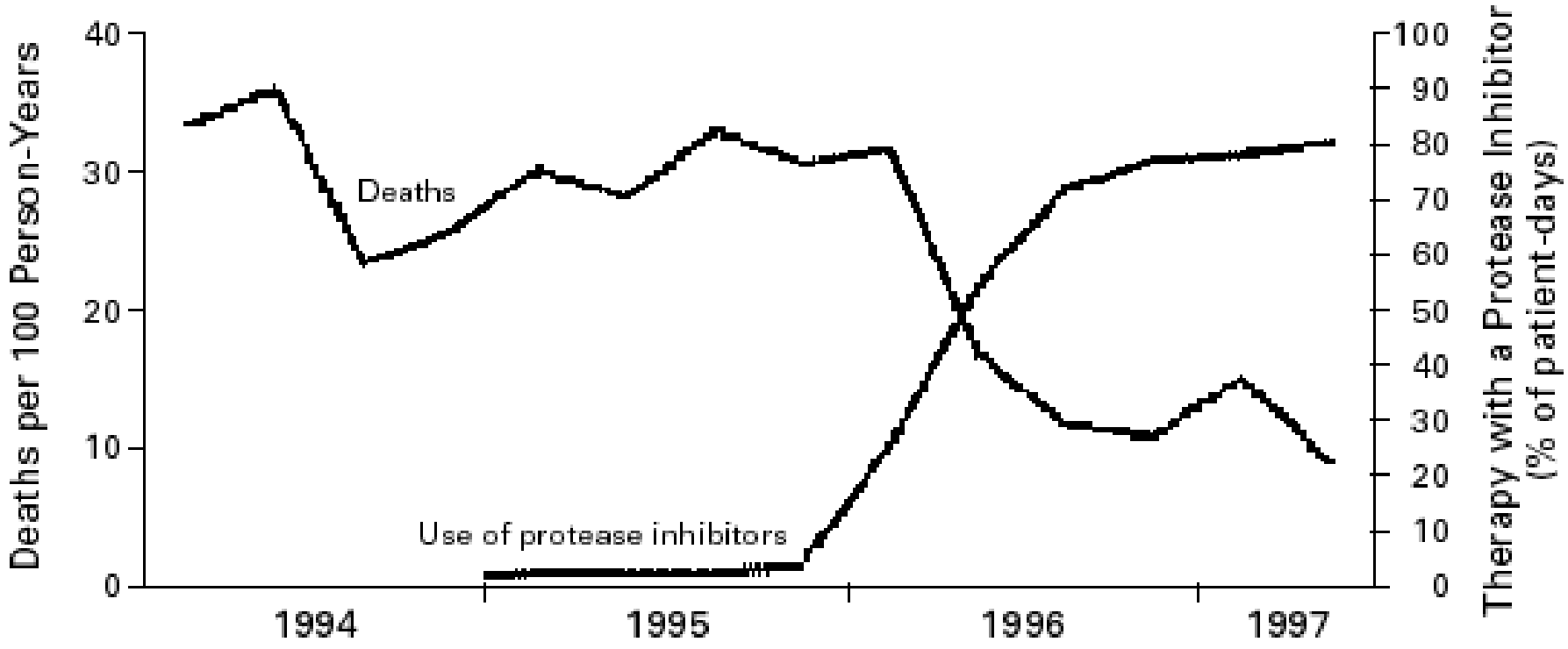
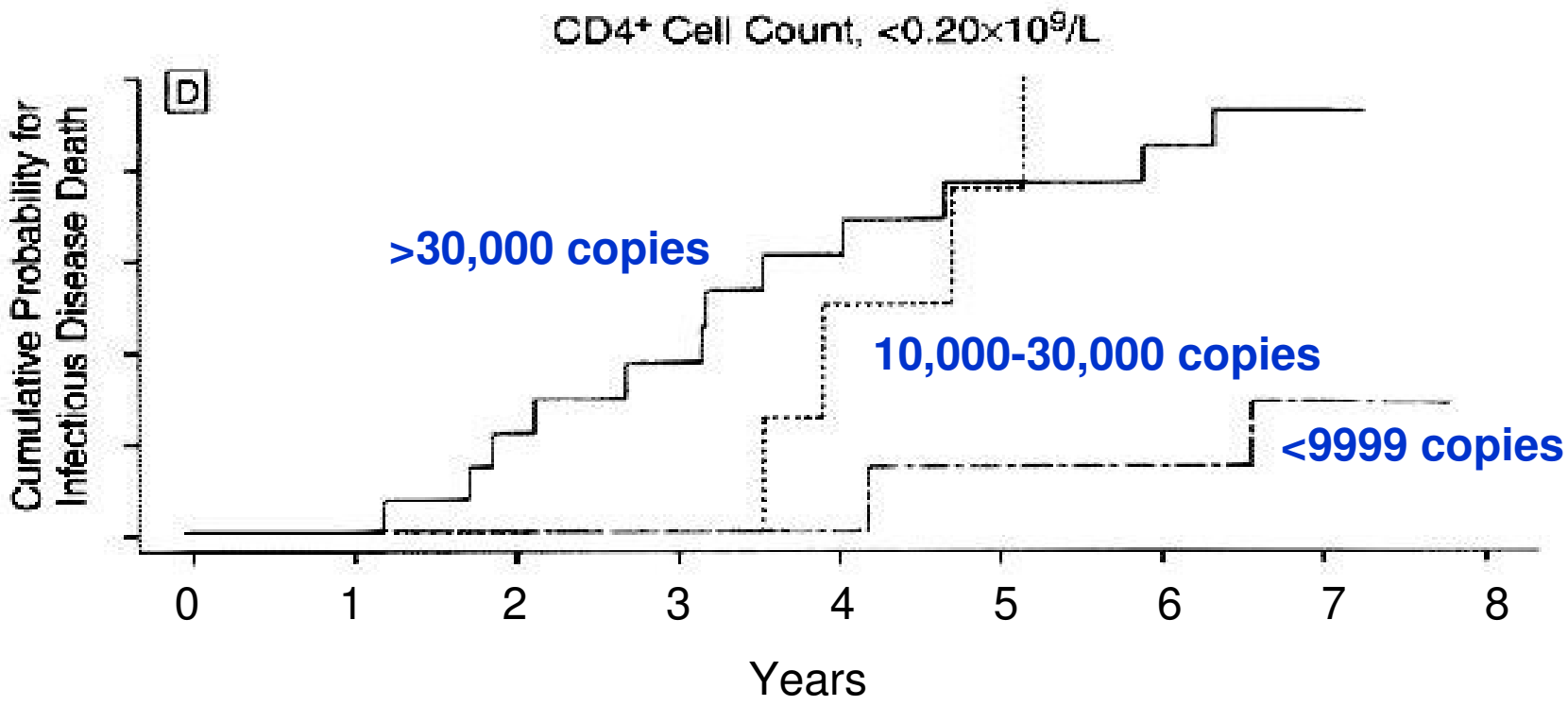
Declining Morbidity and Mortality among Patients with Advanced HIV Infection



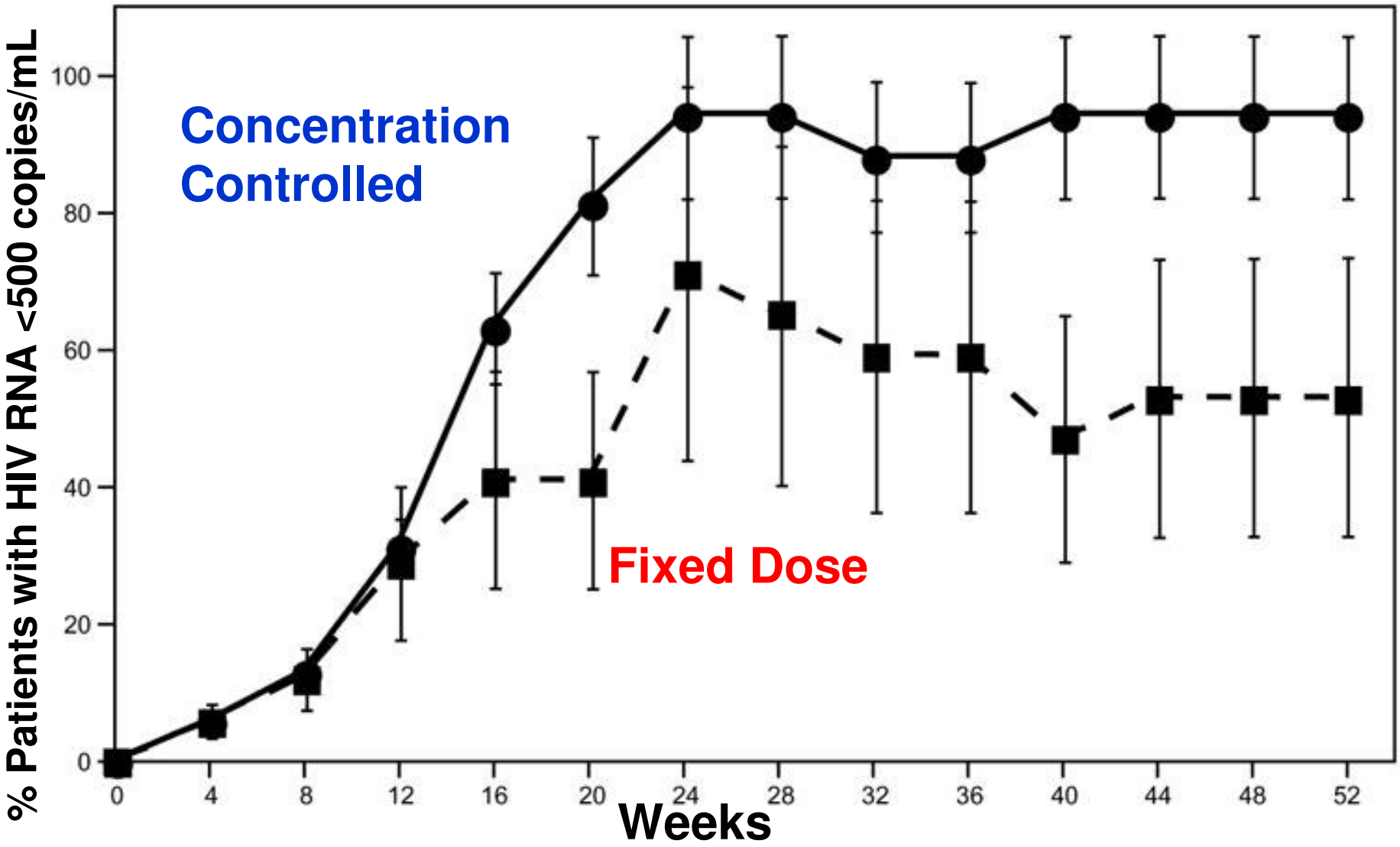
The NEW ENGLAND JOURNAL of MEDICINE

Viral load suppression is predictive of mortality benefit

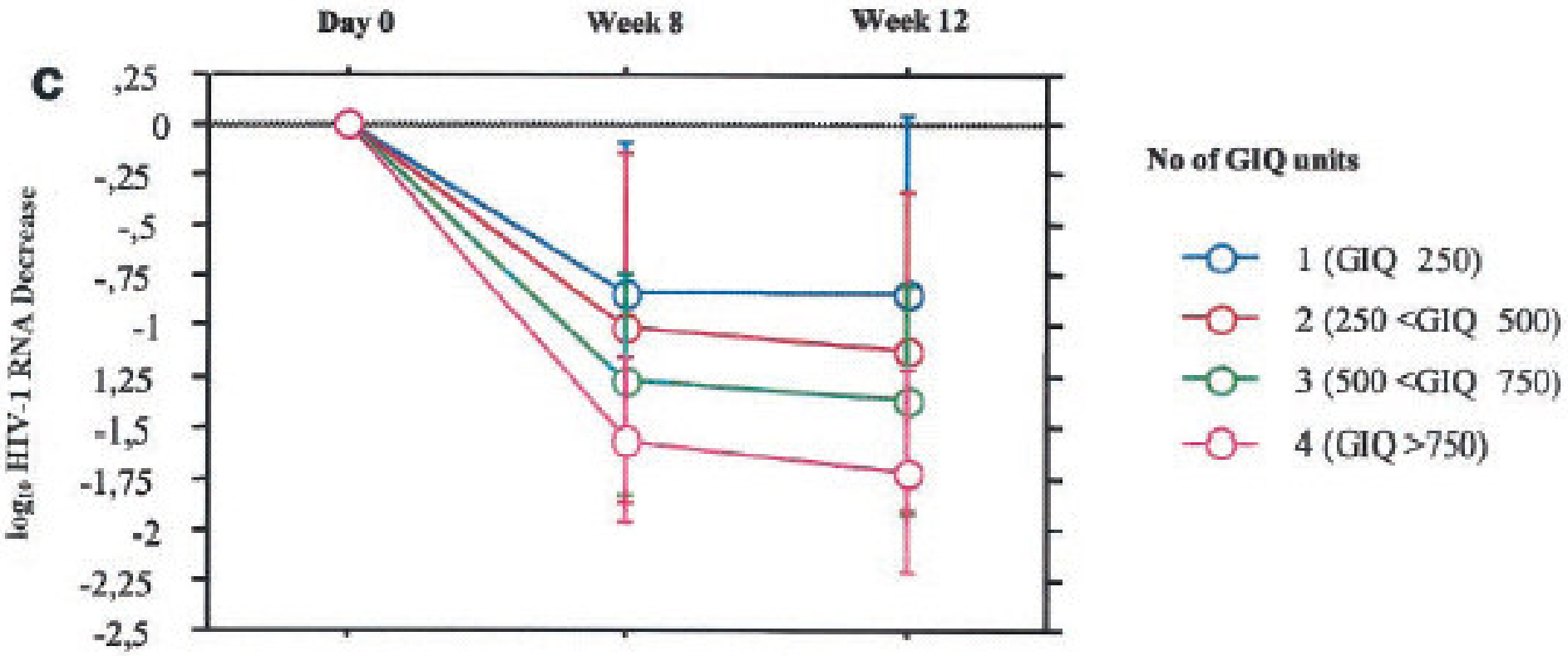


Vlahov et al., Prognostic indicators for AIDS and infectious disease death in HIV-infected injection drug users: plasma viral load and CD4+ cell count. JAMA. 1998 Jan 7;279(1):35-40.

HIV Treatment: Controlling concentrations yields superior benefit than fixed dose



Predictor of Virologic Response to Ritonavir-Amprenavir in HIV Protease Inhibitor Experienced Patients



Antimicrob Agents Chemother 47: 594-600, 2003

Case 1. Tipranavir
Debate at Advisory Committee & Beyond

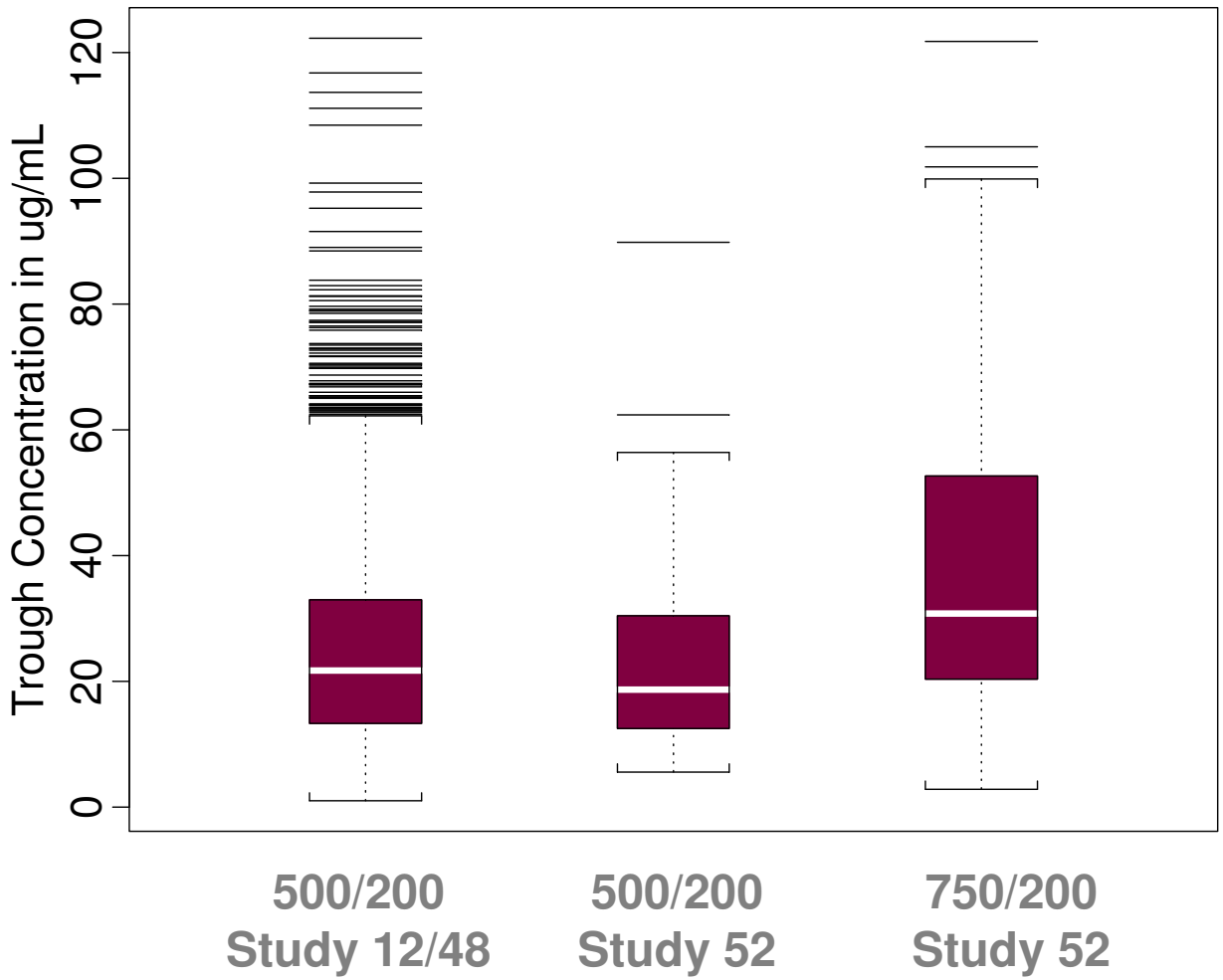
Jenny J. Zheng, Joga Gobburu, Kellie Reynolds

Sponsor: 500 mg twice daily for everyone

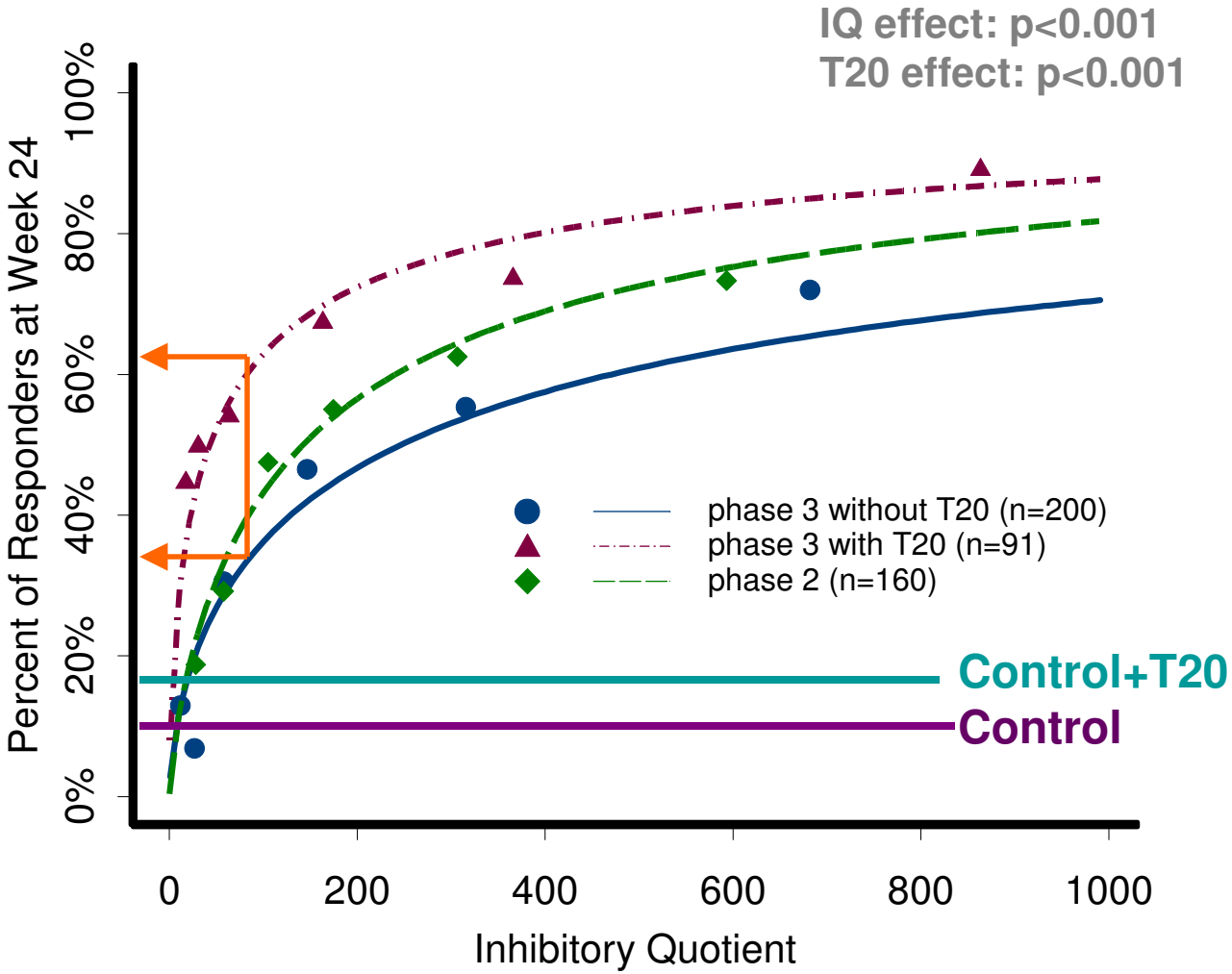
Vs

Individualize dosing based on trough drug concentration & IC_{50} (IQ)

C_{min} in Phase 2 and Phase 3 at Different Doses

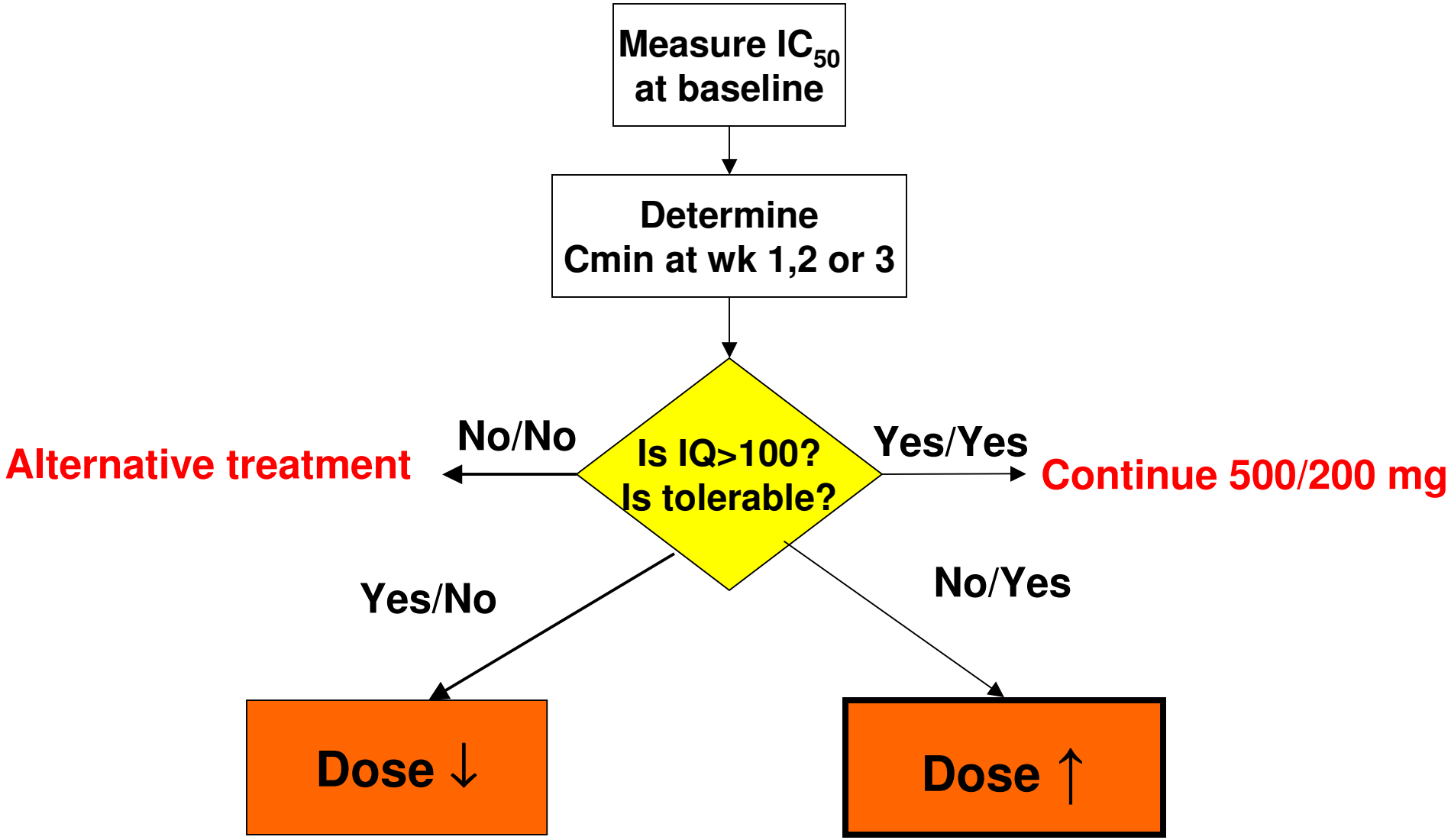


TPV C_{min}, IC_{50}, T20 co-administration significantly influence viral response



For IQ ≥ 100, 54% responded to TPV and 73% responded to TPV+T20
For IQ < 100, 21% responded to TPV and 52% responded to TPV+T20

Possible Therapeutic Drug Monitoring Strategy



Reasons given for not changing

- **Commercial drug assay not available**
- **IC_{50} phenotype too expensive (~$700)**
- **Reimbursement**
- **Prospective trial needed to test hypothesis: HIV protease resistant patients benefit from IQ testing**
- **Implementation variation in clinical practice**
- ***Hidden elephant: marketing***

Dilemma

- **Inside FDA Clinical Pharmacology was proposing changes. Clinical Division (OND) did not agree in this instance, but has agreed to study the issue**
- **Company did not agree**
- **How will the issue be resolved?**
- **How can FDA and clinicians bridge the regulatory……clinical gap to treat (e.g., dose) individual patients, not populations?**

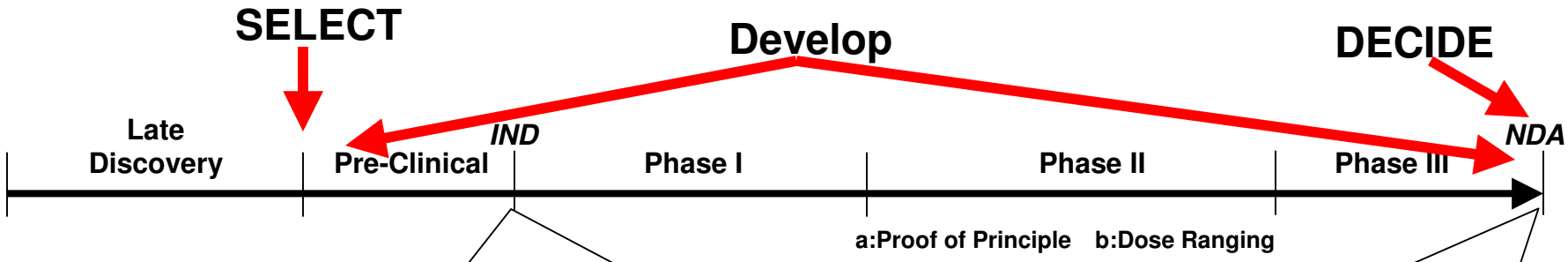
What do we really want?

- **Patients/Heath Professionals**
  - **Health**
  - **Effective drugs @ affordable cost**
- **Drug Companies**
  - **↑ Profits → better drugs & ↑ #**
  - **One dosage regimen for all**
- **FDA**
  - **Promote public health**
  - **↑ Productivity (process & very effective drugs) & ↓ toxicity**
  - **Personalized medicine**

Outline

- How FDA makes decisions
- High attrition, high cost, low productivity
- Model based drug development
  - Disease models
  - Modeling & simulation
- People development

Drug Development & Regulator Process Overview



- IND- application to give drug to humans based upon
  - Toxicology
  - PK/DM
  - Chemistry/Formulation
  - 1st Human protocol

Key question: is this drug safe to administer at doses, rates, routes in 1st protocol?

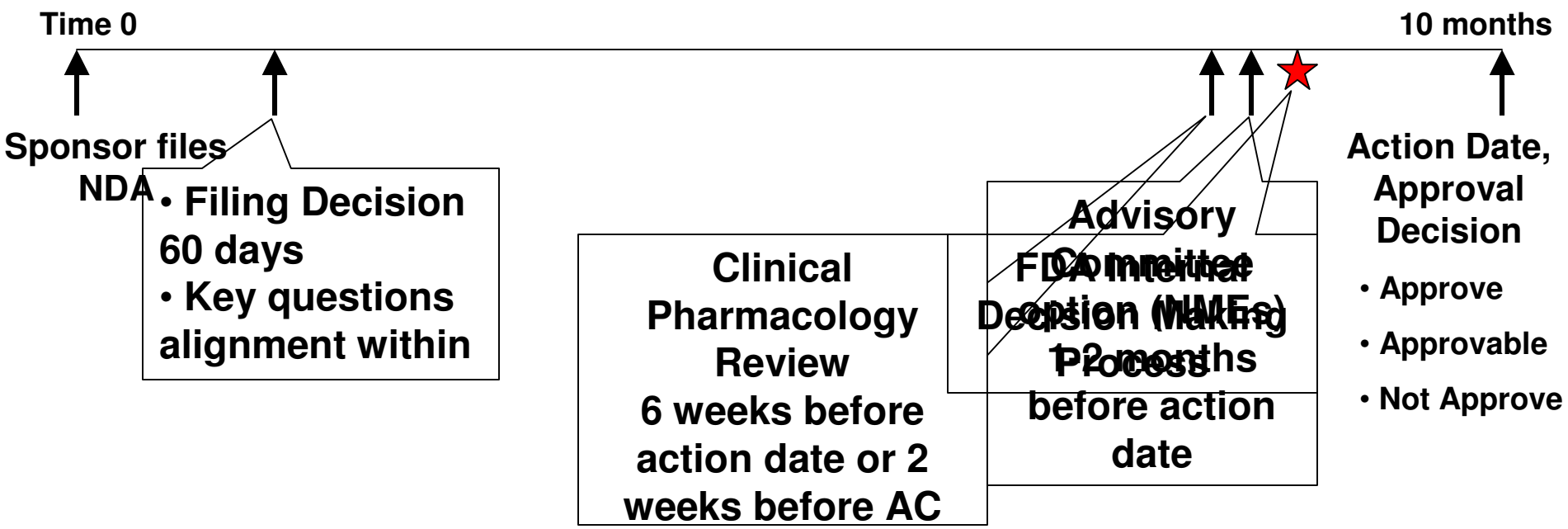
- Pre-IND meeting option
  - Approval endpoints
  - Development strategy
  - Target product profile strategy
  - Dose finding

- NDA-application to market new drug, dosage form, indication
  - IND information + gene tox + carcinogenicity
  - Clinical trial evidence of efficacy & safety

NDA (new drug application) Review Process

3 NDA Types

- Standard-10 month clock
- Priority-6 month
- Accelerated-<10 month, oncology/HIV unmet medical needs



NDA Decision Process

Regulatory Briefing option (CDER senior staff)

↑

Office Director (MD) (NCEs)

↑

Therapeutic Division Director (MD) (e.g., Cardiorenal)

↑

OND Team Leader (MD)

↑

NDA Review Team

- Physician
- Clinical Pharmacologist
- Statistician
- Pharm/Tox
- Chemist
- Project manager

} Advisory recommendations

Reasons for Poor Decisions

(Definition: an outcome which should/could have been anticipated)

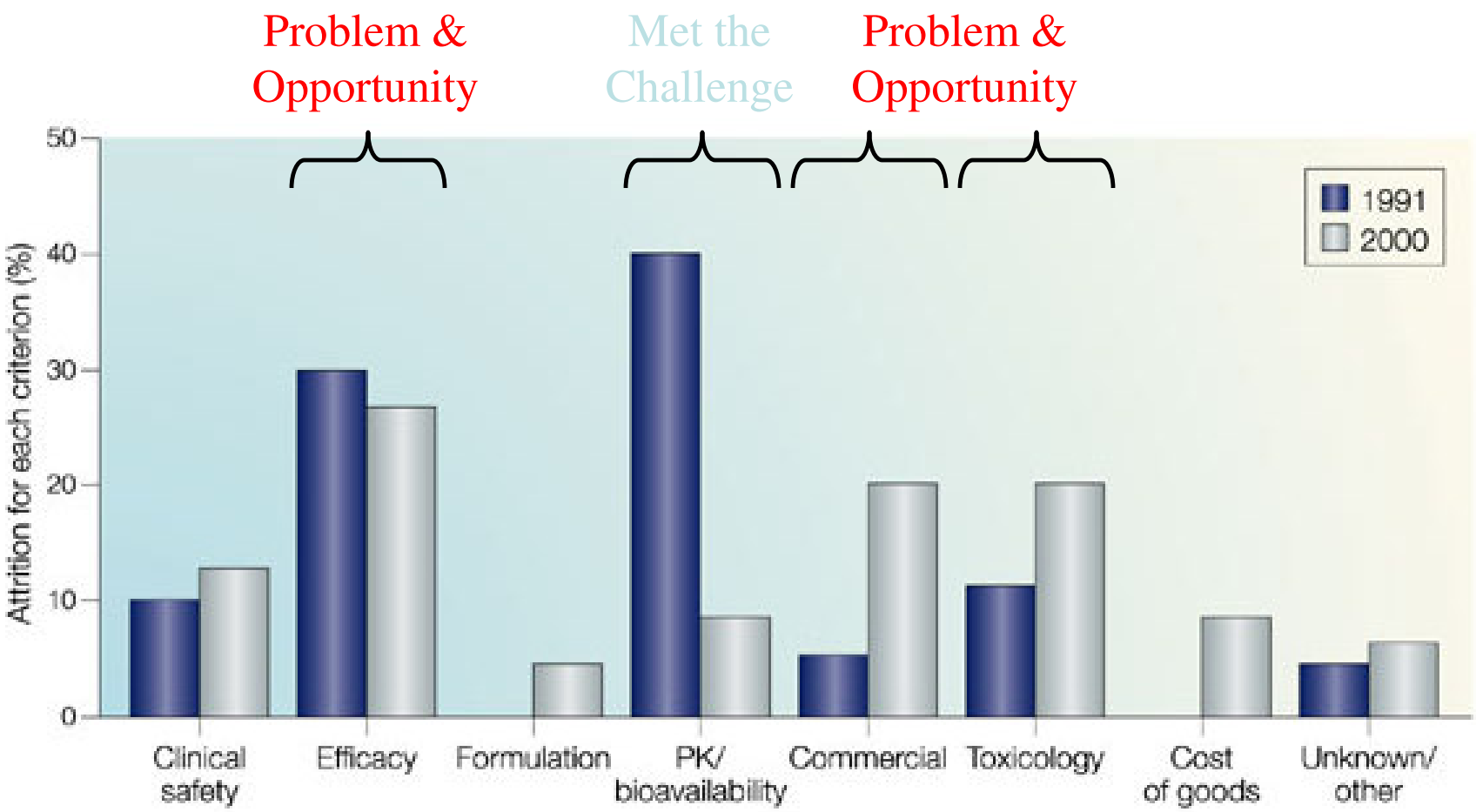
- Conspiracy of optimism
- Framing the problem too narrowly to bring it inside my own comfort zone
- Not involving the right people
- Avoiding uncertainty
- Ignoring information I do not understand
- Being attached to 'sunk costs' – high spent development costs
- Ignoring risks
- Assuming no uncertainty in potential outcomes
- Making decision alone

BIAS

Hammond, Keeney, Raiffa. Smart Choices Harvard Business School Press, 1999

Causes of Attrition (1991 & 2000)

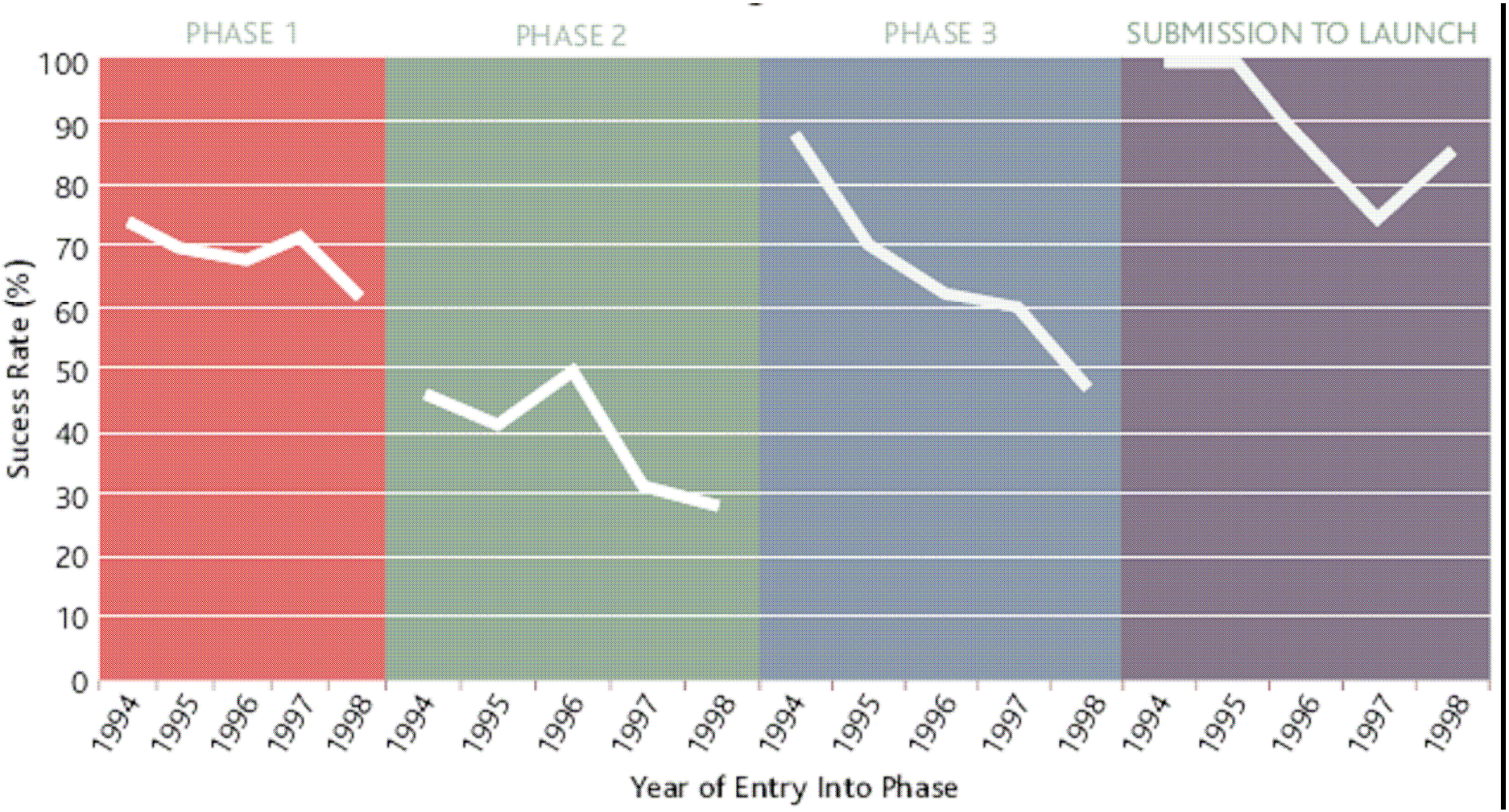
10 Big PhRMA Companies



Kola and Landis. Nature Reviews Drug Discovery 2004;3:711-6.

1 Driver for Clinical Trial M&S

Declining Success Across Clinical Phases



Science 309:726, 2005

50% Clinical Trial Failure Rate: Is it true? What to do?

True +	True -	False +	False -

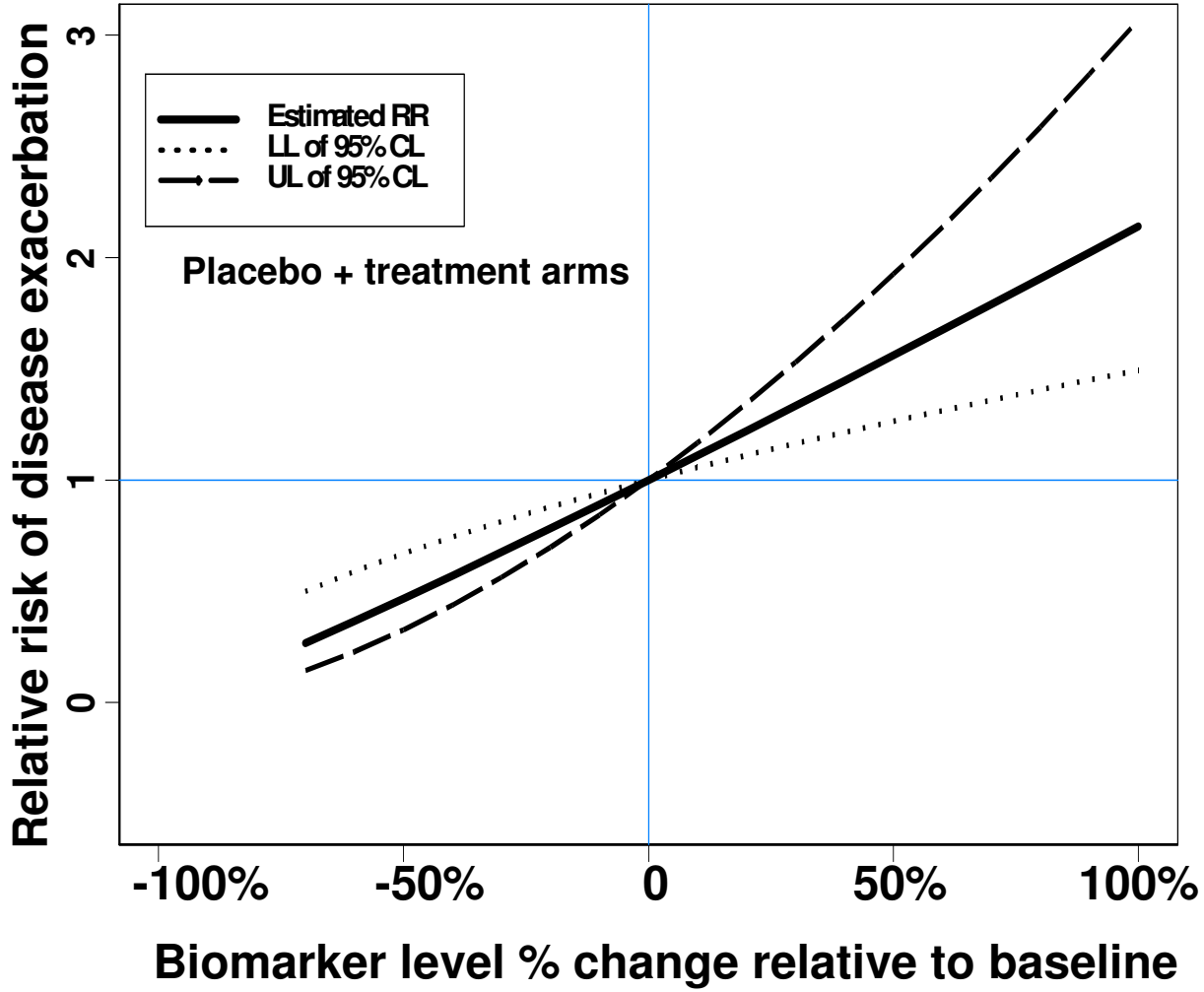
OBJECTIVE: ↑ ↓ ↓ ↓

Acc[illegible]nown failur[illegible]s (prior informa[illegible]n clinical tr[illegible]ign

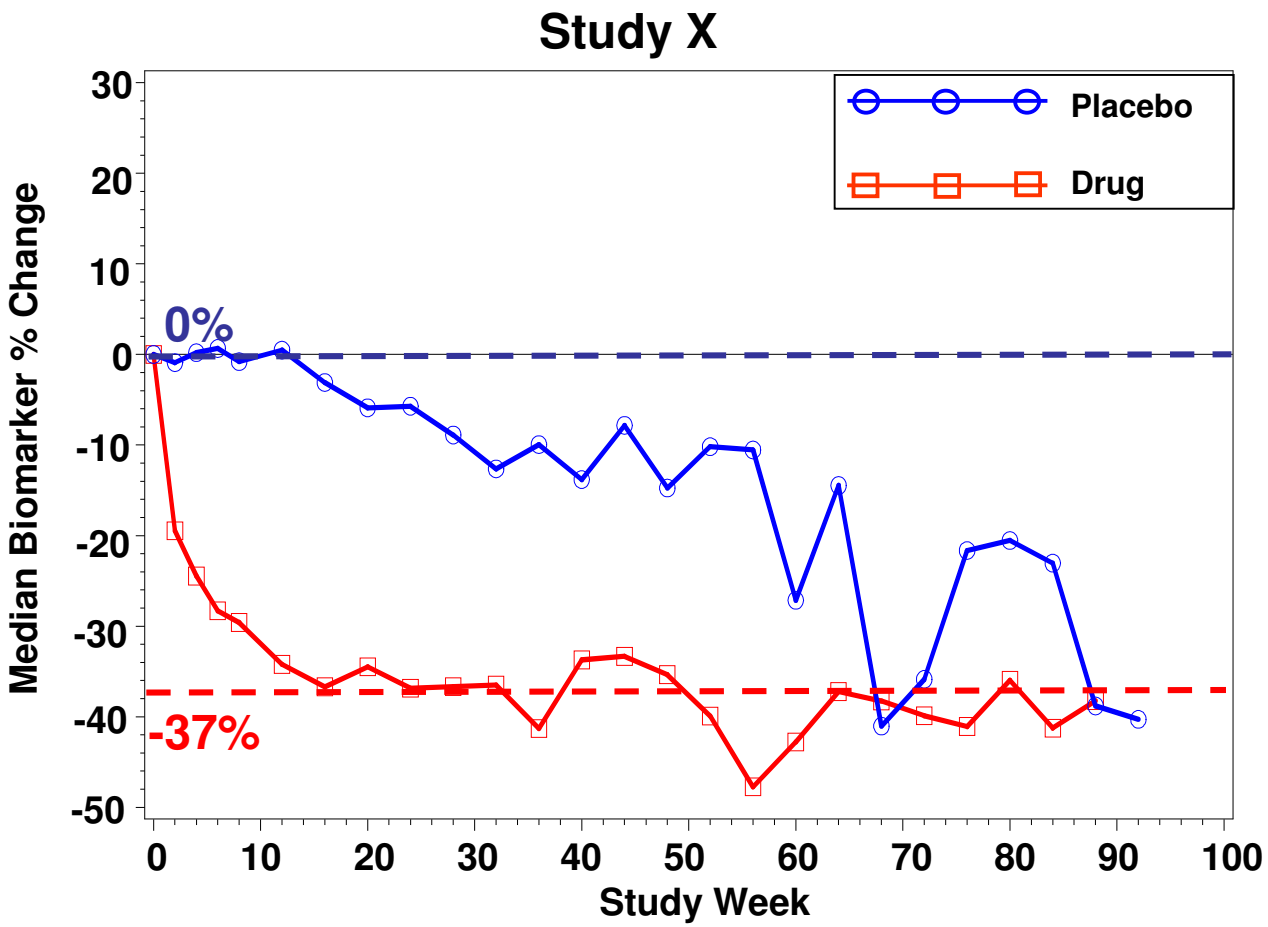
Root Cause

- Ø Efficacy
- ↑ Toxicity
- Placebo
- Baseline
- Dropouts
- Patient Selection

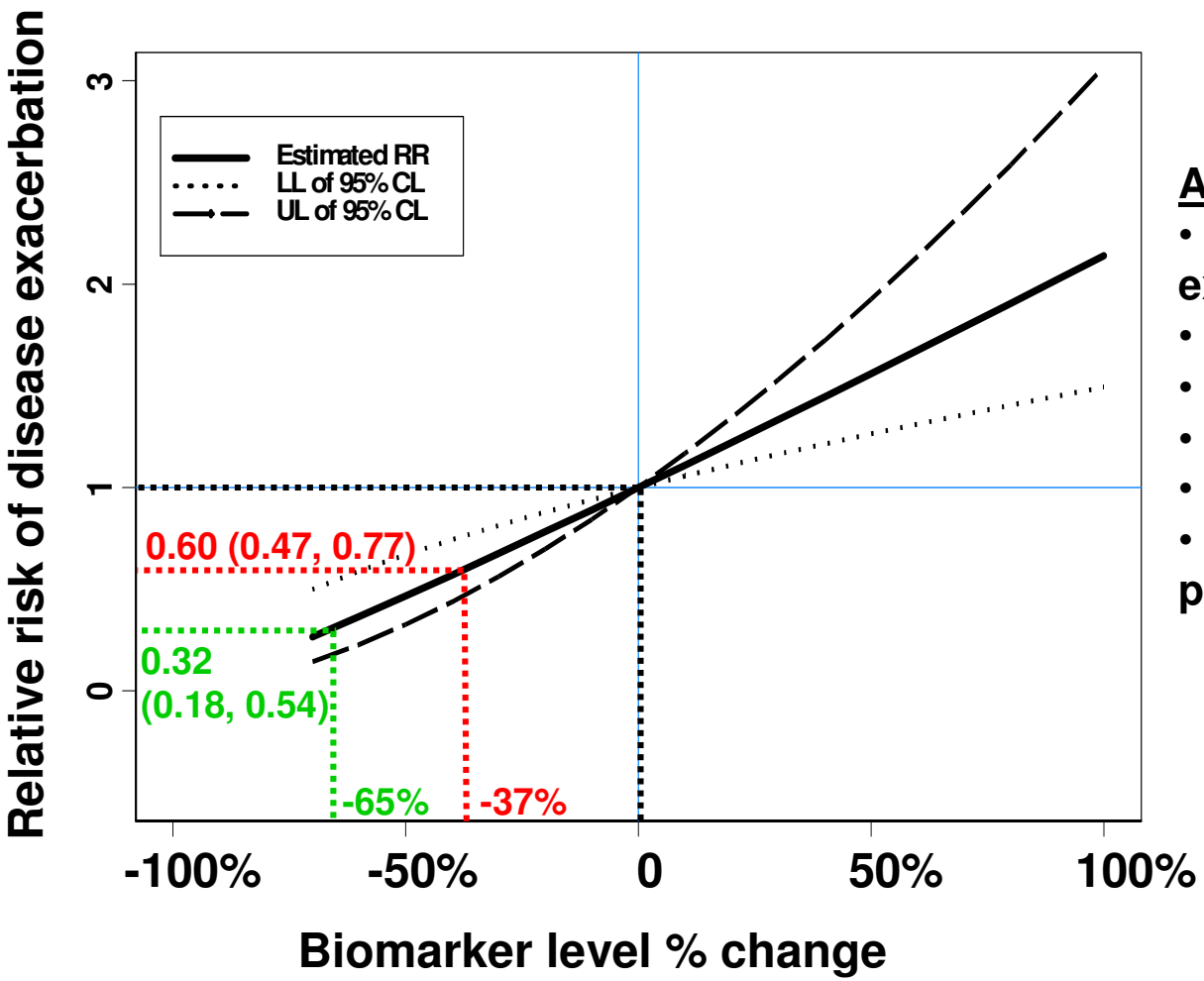
Case 2: Reducing Disease Biomarker Concentration → Lower Risk of Disease Exacerbation Irrespective of Treatment



Drug Reduces Biomarker Levels (Median)



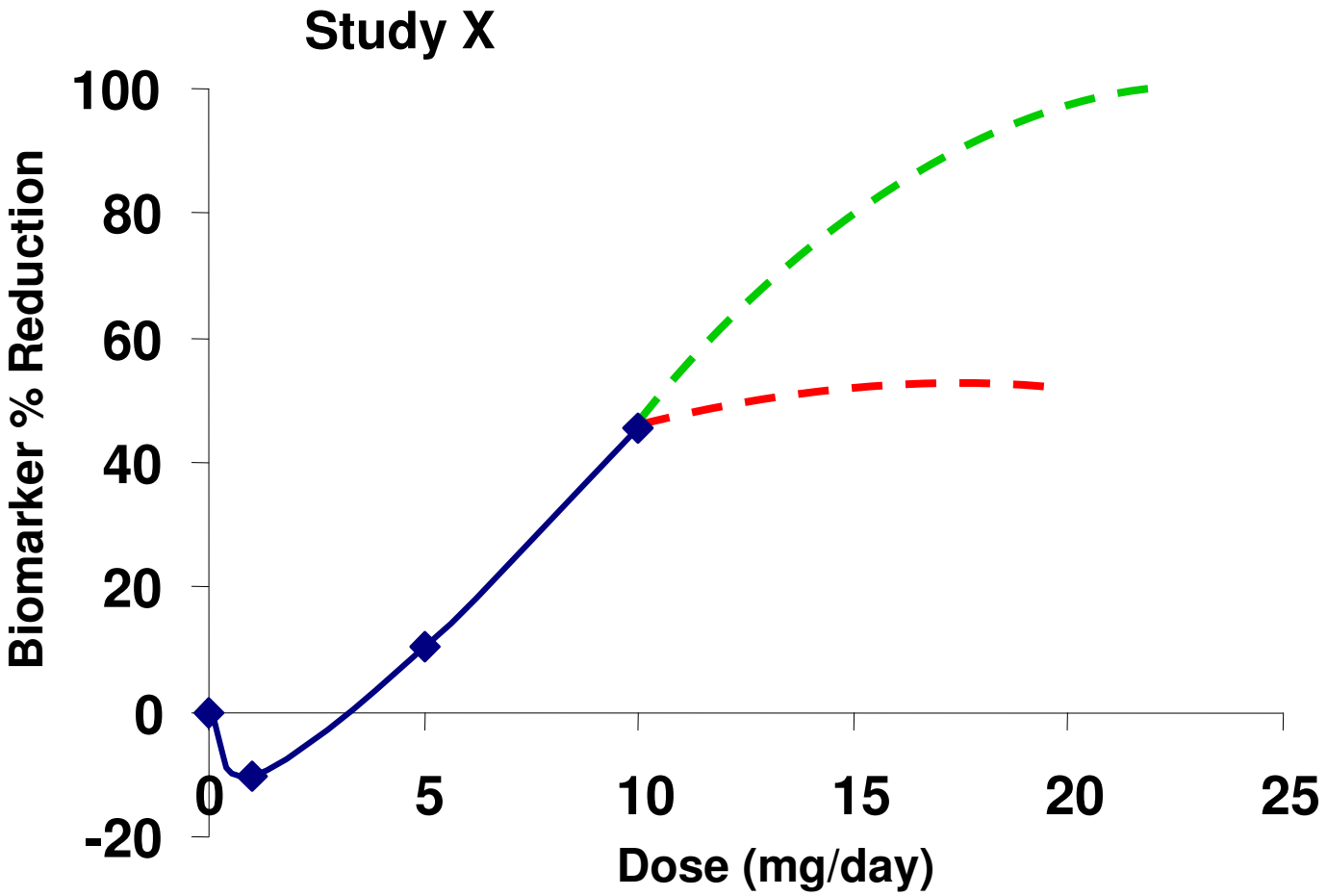
Greater Reduction in Biomarker Level Is Required for Significant Benefit



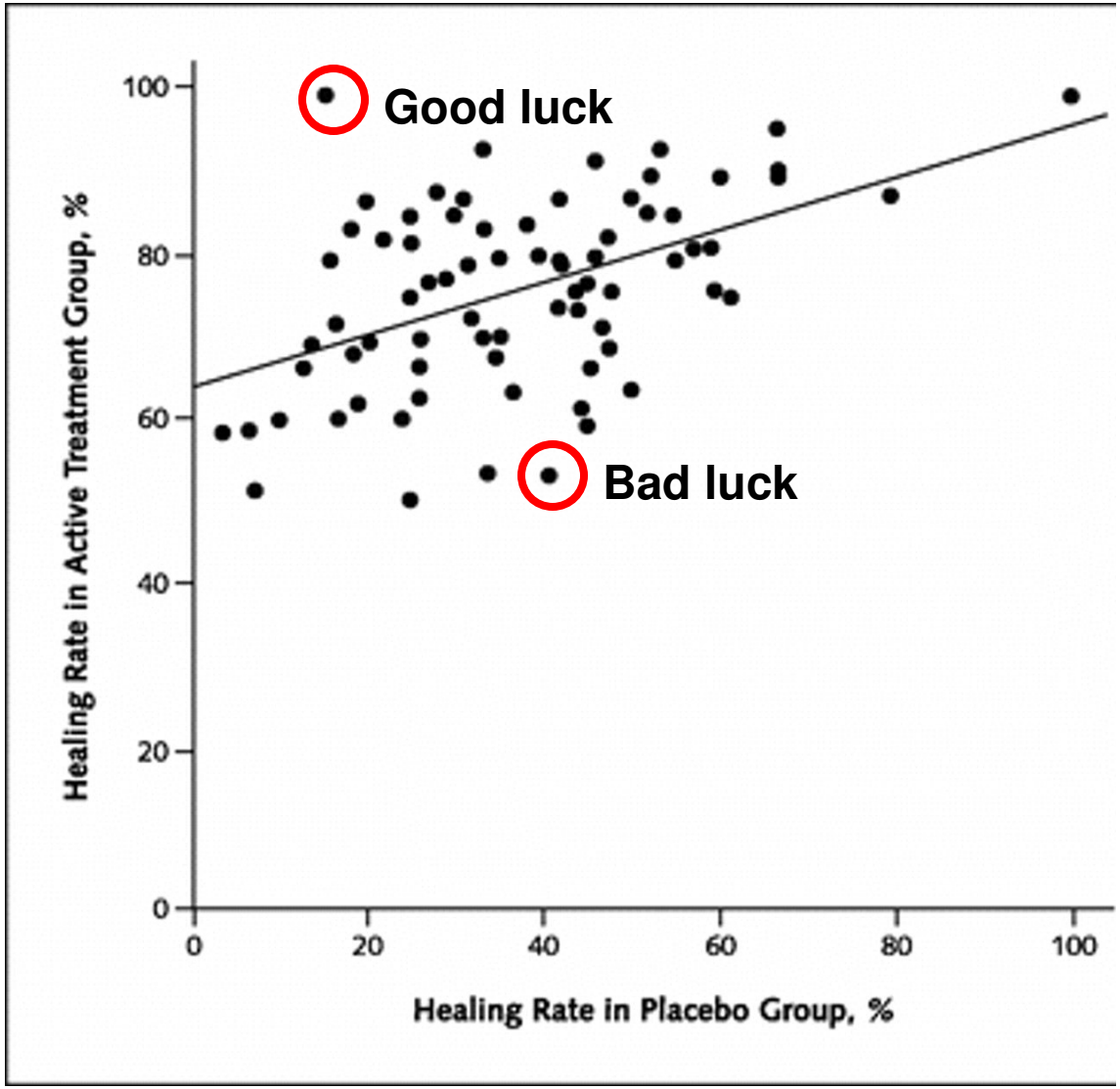
Assumptions

- Bm predicts disease exacerbation
- Largest slope
- Bm no change in placebo
- Bm↓ 37% 2° Drug
- n=150/arm
- 22% exacerbation with placebo

Higher Doses Associated with Greater Biomarker ↓

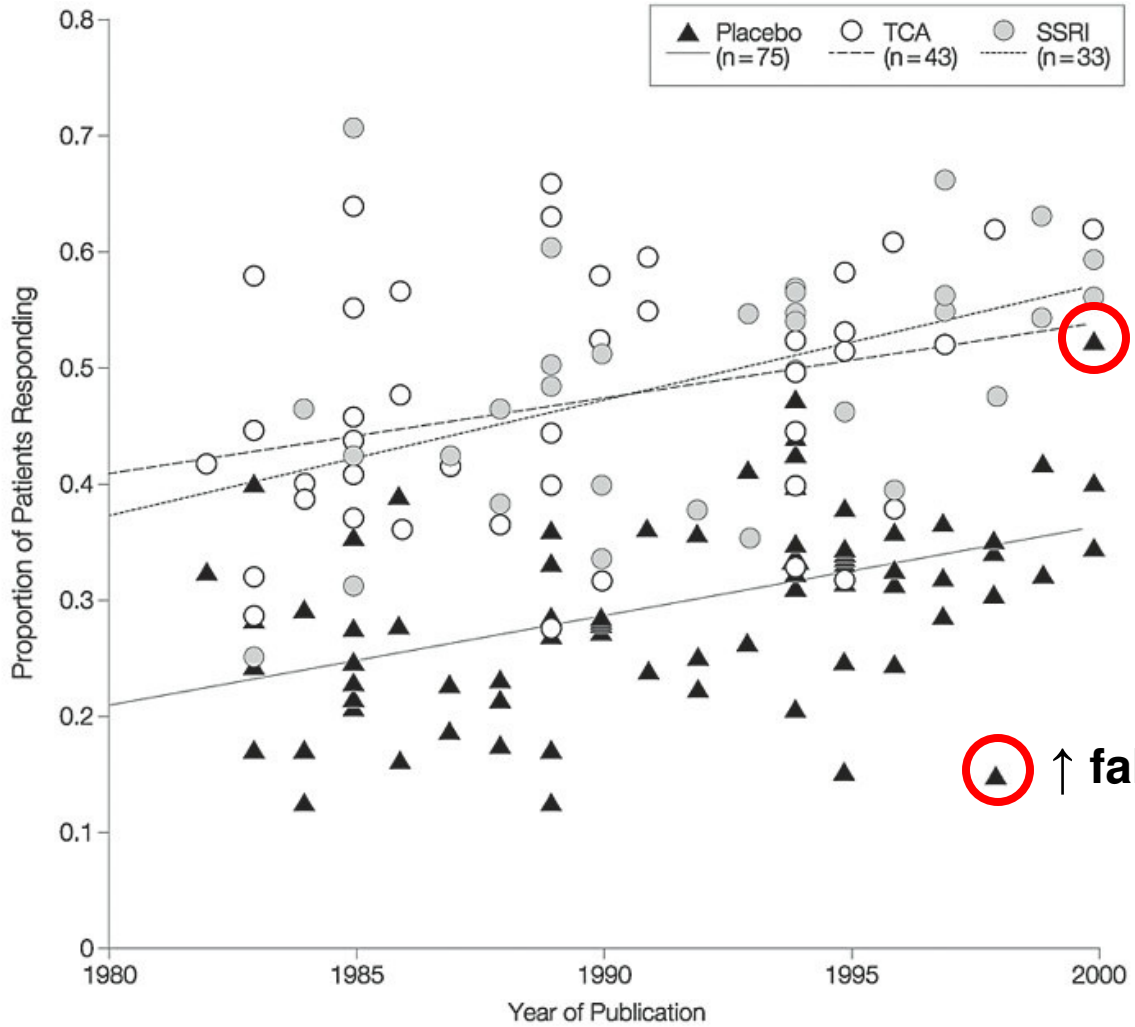


Duodenal Ulcer Healing Rate in Active (Cimetidine or Ranitidine) vs Placebo (n=83 studies)



Moerman, D. E. et. al. Ann Intern Med 2002;136:471-476

Placebo Response in Depression



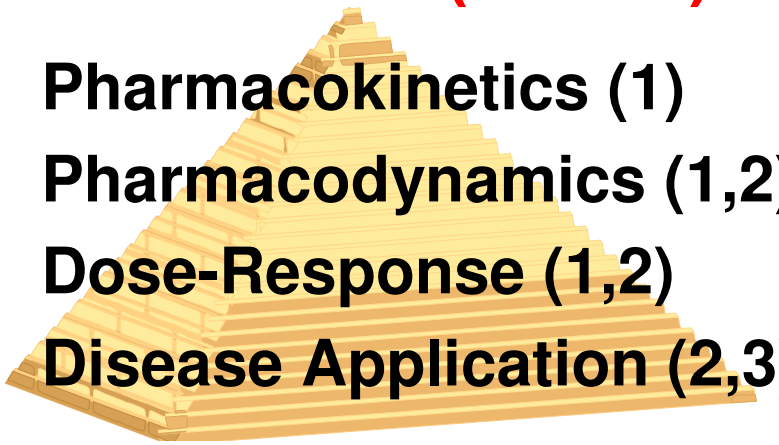
↑ trial failure risk

↑ false positive risk

JAMA 287: 1840-7, 2002

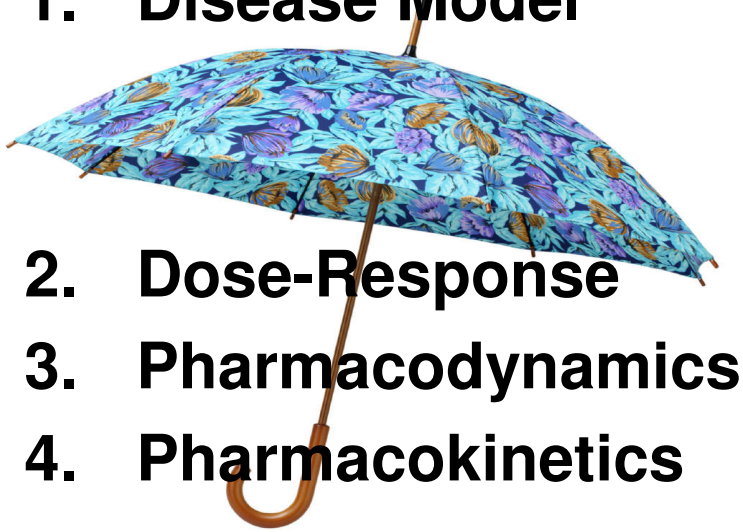
Clinical Drug Development
Shifting Paradigm

Historical, Discipline-based Model (Phase)



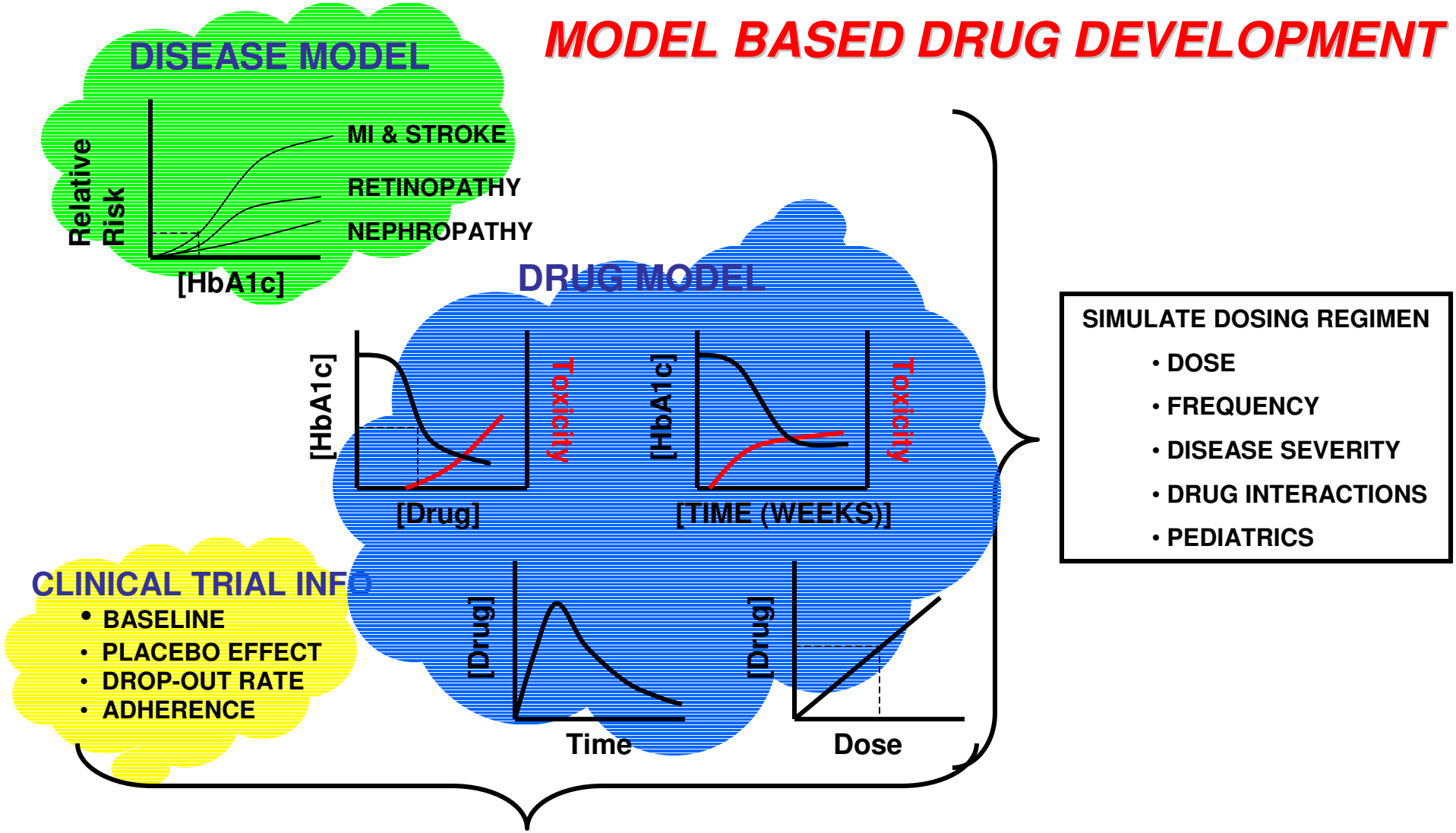
1. Pharmacokinetics (1)
2. Pharmacodynamics (1,2)
3. Dose-Response (1,2)
4. Disease Application (2,3)

Contemporary, Therapeutics-based Model



1. Disease Model
2. Dose-Response
3. Pharmacodynamics
4. Pharmacokinetics

MODEL BASED DRUG DEVELOPMENT



IMPACT OPPORTUNITIES- MODEL & SIMULATE KEY DECISIONS

COMPANY → TRIAL DESIGN (2, 3), GO/NO GO, LABELING, FORMULATION, COMBO'S, PEDS

FDA → TRIAL DESIGN (2, 3, 4), NDA APPROVAL (BENEFIT/RISK, DOSING REGIMEN), LABELING, APPROVAL CRITERIA (GUIDANCE REVISION), FORMULATION, COMBOS, QT STUDIES, PEDIATRIC WRITTEN REQUESTS

Biomarker Model
The Ultimate in Personalized Medicine

Patient Drug Response ≈ **Disease Gene Marker** + **Biological Markers (Efficacy, Toxicity) N1+N2** + **Drug Markers Gene Conc IC_{95}** + **Imaging Marker**

- Disease present?
- Receptor subtype present?

2D6 cypP450 genoty

- Cell, protein, antibody, small MW chemical, physical measure
- linked to endpoint outcome for efficacy or toxicity

- [Drug]p
- Inhibit
concentration 90%
- e.g., antiviral protease inhibitors

- PET, MRI,..
- Physical direct evidence for change

Modeling & Simulation Influences All Lives Today

- Weather forecasting
- Global warming scenarios
- Finance
- Engineering
  - Plant design
  - Product design
    - Airplanes
    - Cars-crash testing
    - Bridges
    - Microprocessors
    - Widgets
  - Traffic flow-roads
- Homeland Security
  - Disaster preparedness scenarios
  - Plague
- Military
- Space
- Energy
- Medical
  - Rx patients
    - Surgery
    - Diagnostics (MRI,…)
  - Education
  - Devices (hip, knee,..)
  - Drugs
    - Molecular design/receptor
    - Formulation
    - Manufacturing
    - Marketing
  - Forensic reconstruction

The Ultimate 'Learn-Confirm' Paradigm

Boeing JSF Modeling and Simulation Breakthroughs Reduce Program Risk, Cost

SEATTLE, Wash., Oct. 04, 2001 -- Boeing today unveiled details of a comprehensive modeling and simulation architecture that assures new levels of affordability. Demonstrated during the Joint Strike Fighter program's concept demonstration phase, these improvements will make the Department of Defense's long-standing vision of simulation-based acquisition a reality.

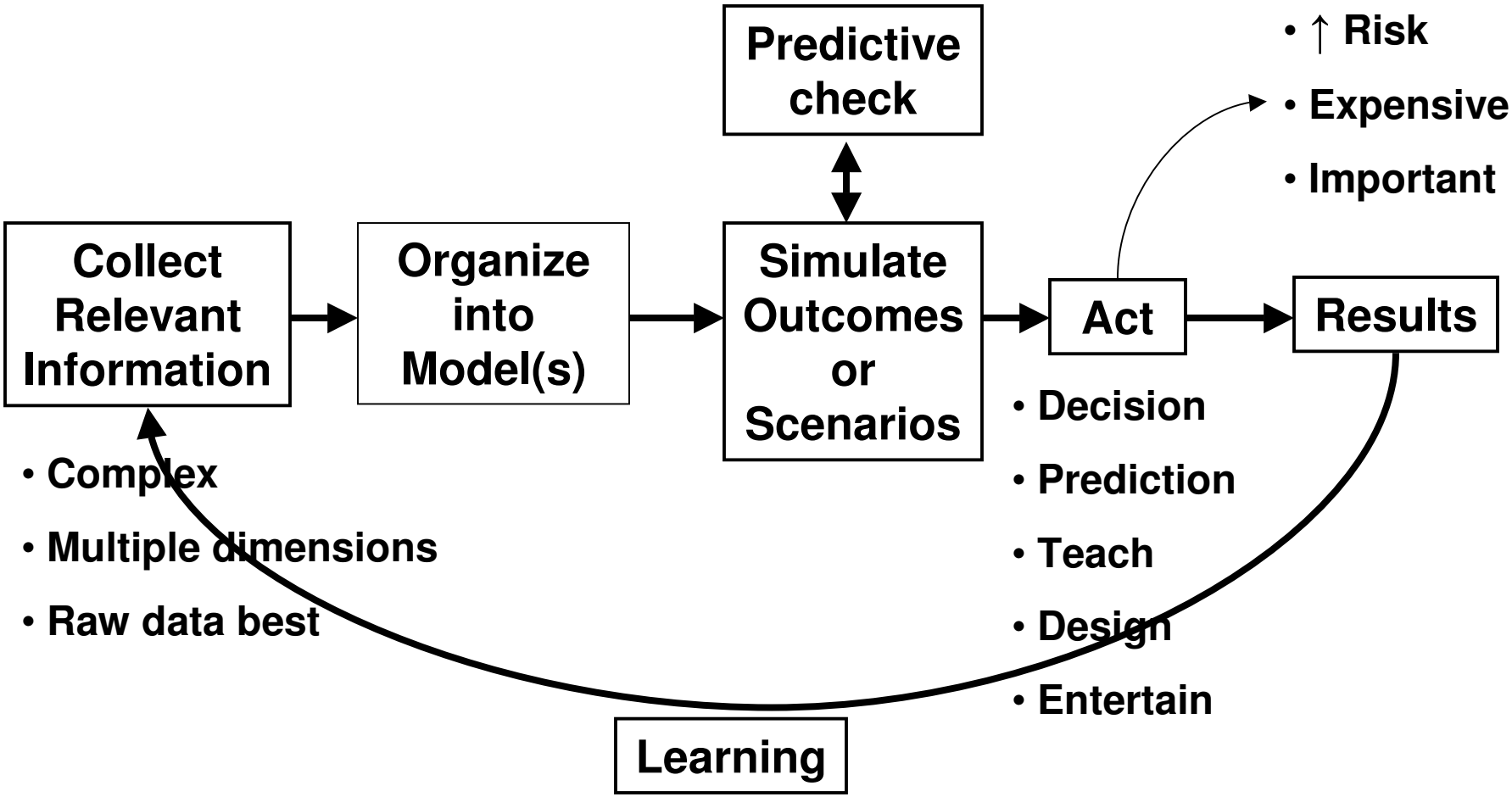
Combining benchmarks achieved on its 777 and Next-Generation 737 commercial aircraft, C-17 airlifter, Apache helicopter and other programs, the new Boeing JSF architecture incorporates what previously were separate, stand-alone modeling and simulation tools into an overall integrated system.

"The importance of modeling and simulation in reducing risk can't be emphasized enough," Statkus said. "We were able to eliminate the majority of bugs before we ever built or flew the X-32 aircraft. Excellent software models and revolutionary control law development made the changeover from the lab to flight test incredibly simple.

Modeling & Simulation
Why?

- **Decrease bias & risk in decisions**
- **Overcome complexity (simultaneously thinking about many factors influencing outcome)**
- **Increase quality**
- **Decrease cost**
- **Decrease time**

Modeling & Simulation Process



Case 3. Type 2 Diabetes Drug

Jaya Vaidyanathan, Hae-Young Ahn, Dong Yim, Jenny Zheng, Yaning Wang, Joga Gobburu, Todd Sahlroot, David Orloff

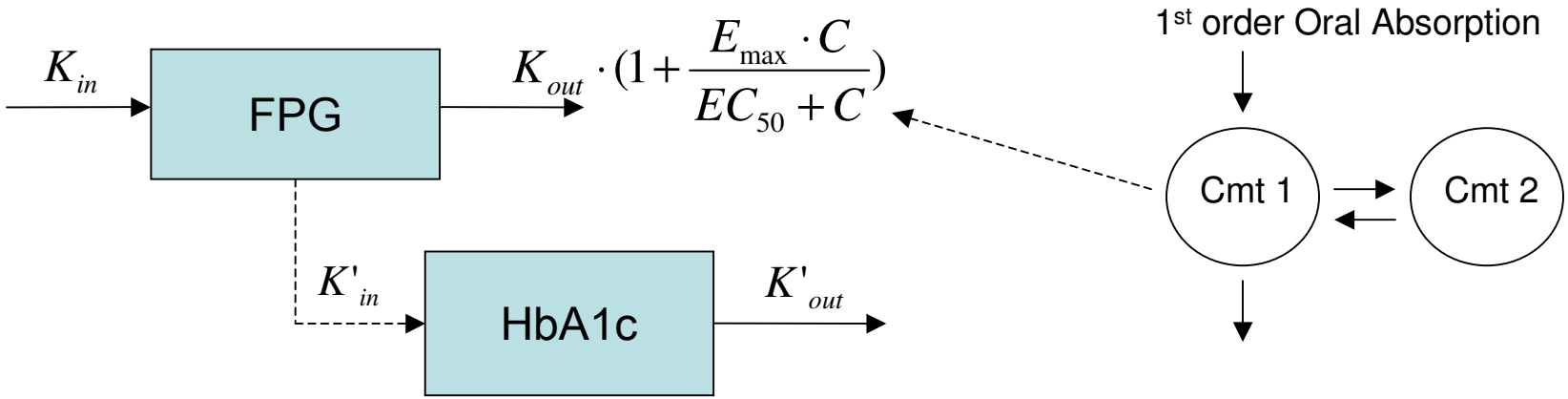
- **Topic: Phase 3 trial design when 3x genotypic drug clearance difference**
- **UGT2B15 metabolic enzyme frequency distribution (N=374)**
  - ***1/*1 21%**
  - ***1/*2 52%**

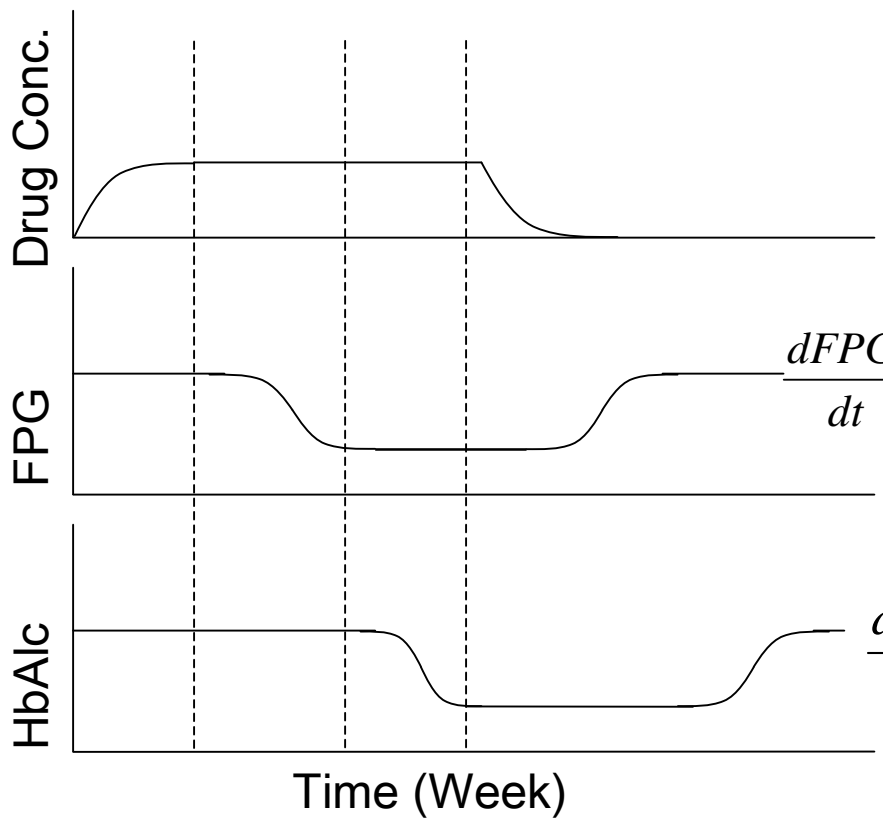
  } **Extensive metabolizers (EM's)**
  - ***2/*2 27%** **Poor metabolizers (PM's)**
- **Indication: Type 2 diabetes mellitus**
- **Mechanism of action: $PPAR_{x,y,z}$ agonist**
- **↓ FPG & HbA1c**
- **↑ weight**

Modeling Strategy

- Pharmacokinetics
  - Phase 1 data for population PK model
  - Phase 2 data for model update
- Pharmacodynamics (FPG and HbA1c)
  - Model from FDA clinical trial data
  - Simultaneous modeling FPG and HbA1c
  - Models updated with sponsor data

Diabetes





$$\frac{dFPG}{dt} = K_{in} - K_{out}(1 + \frac{E_{max} \cdot C}{EC_{50} + C}) \cdot FPG$$

$$\frac{dHbA1c}{dt} = K'_{in} \cdot FPG - K'_{out} \cdot HbA1c$$

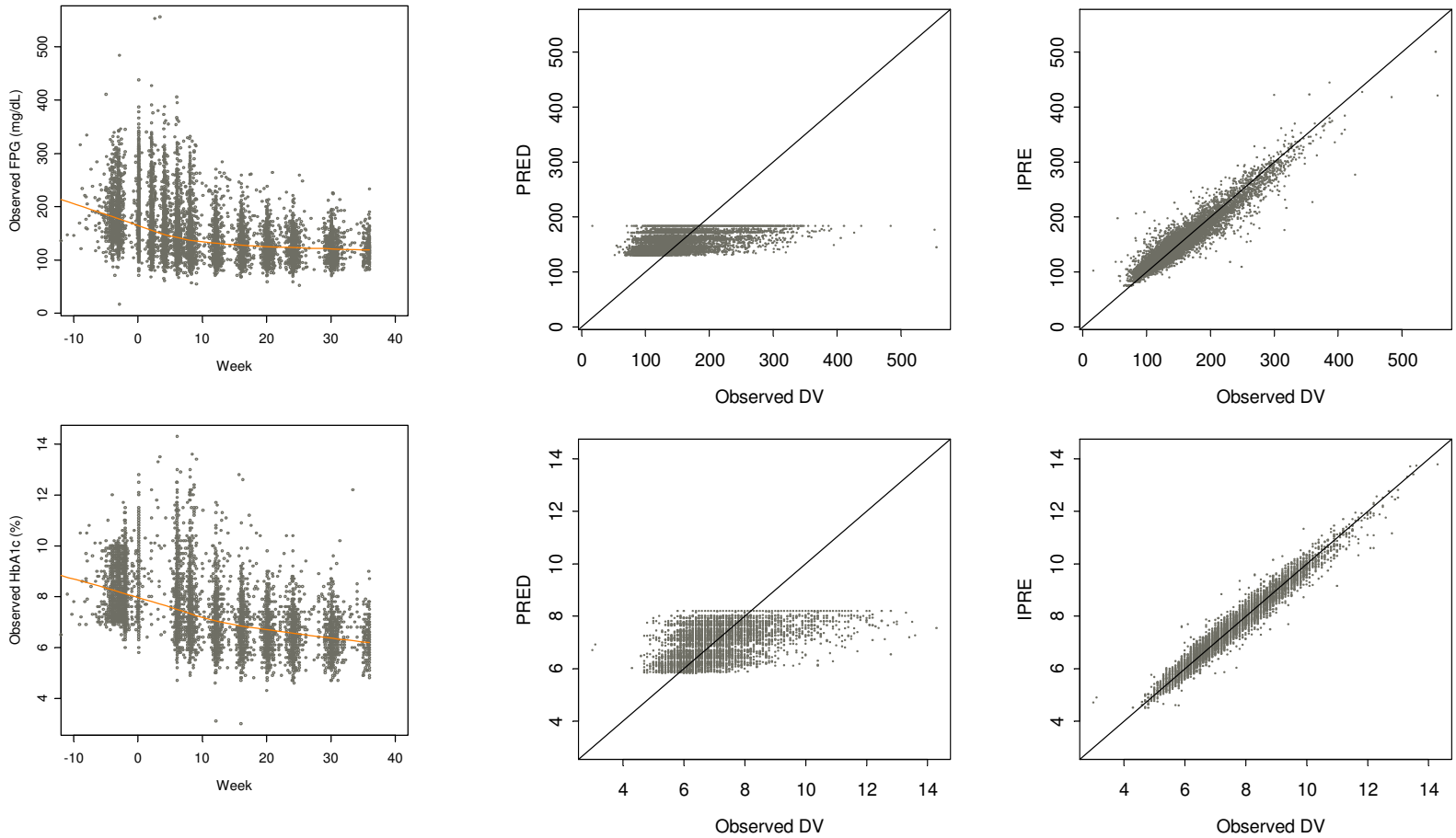
Bill Jusko's model

Modeling Results for FPG & HbA1C

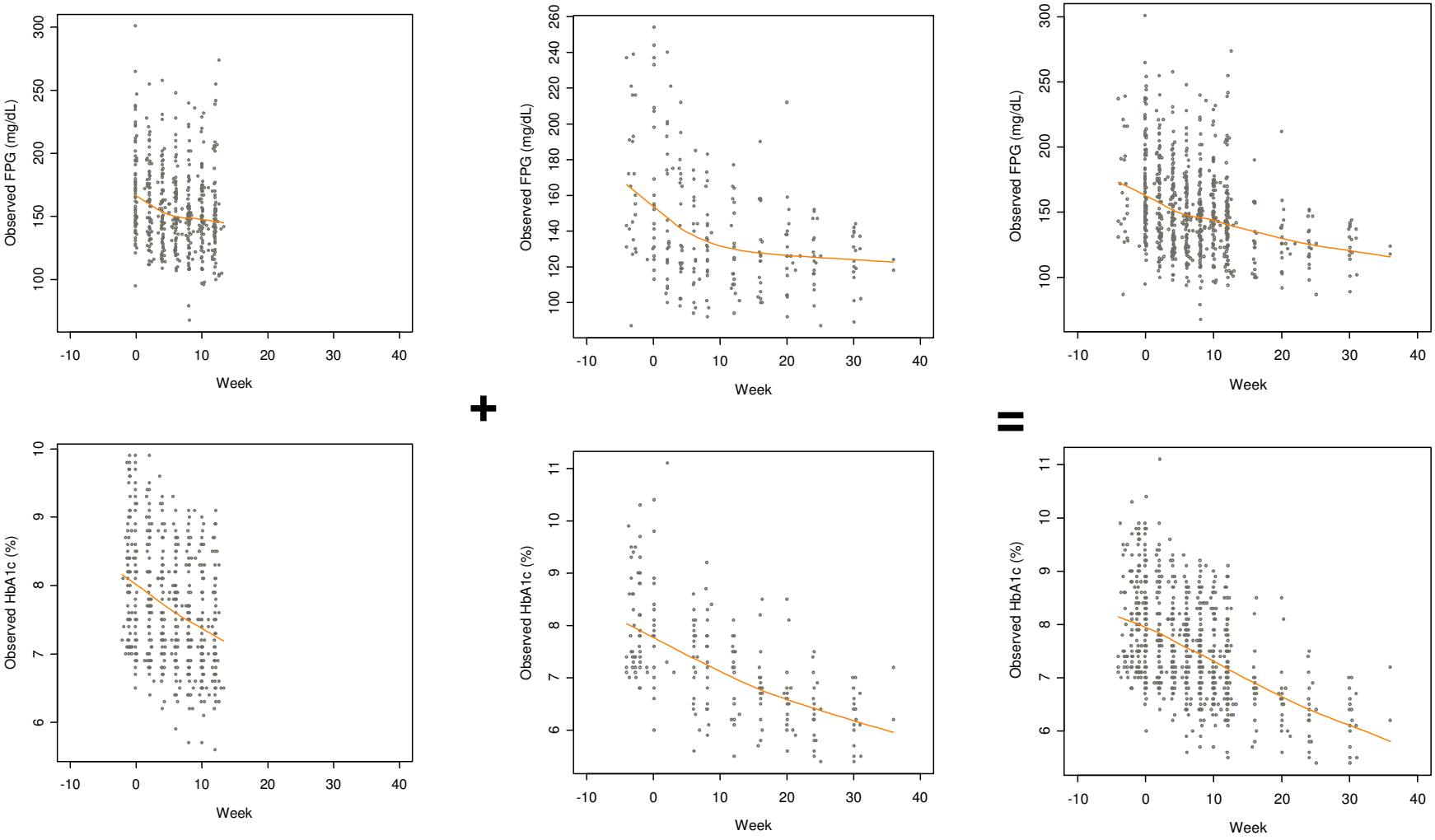
Drug X in 1,000 patients

FPG

HbA1c



We made up a Hybrid Dataset

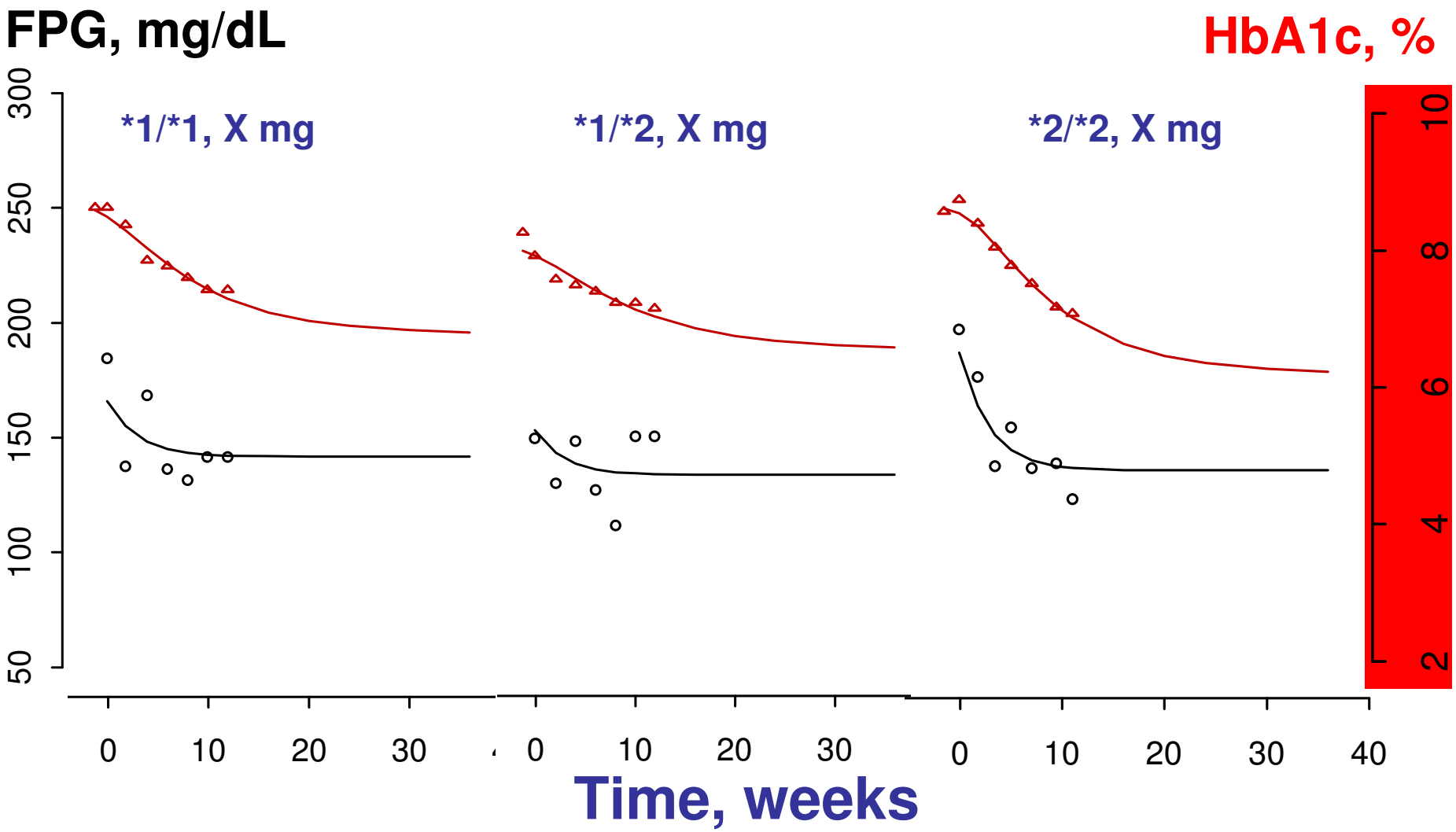


Drug X (Sponsor) in 72 patients

Drug X (other) in 28 patients

Hybrid dataset in 100 patients

Model Fits
(individual patients)



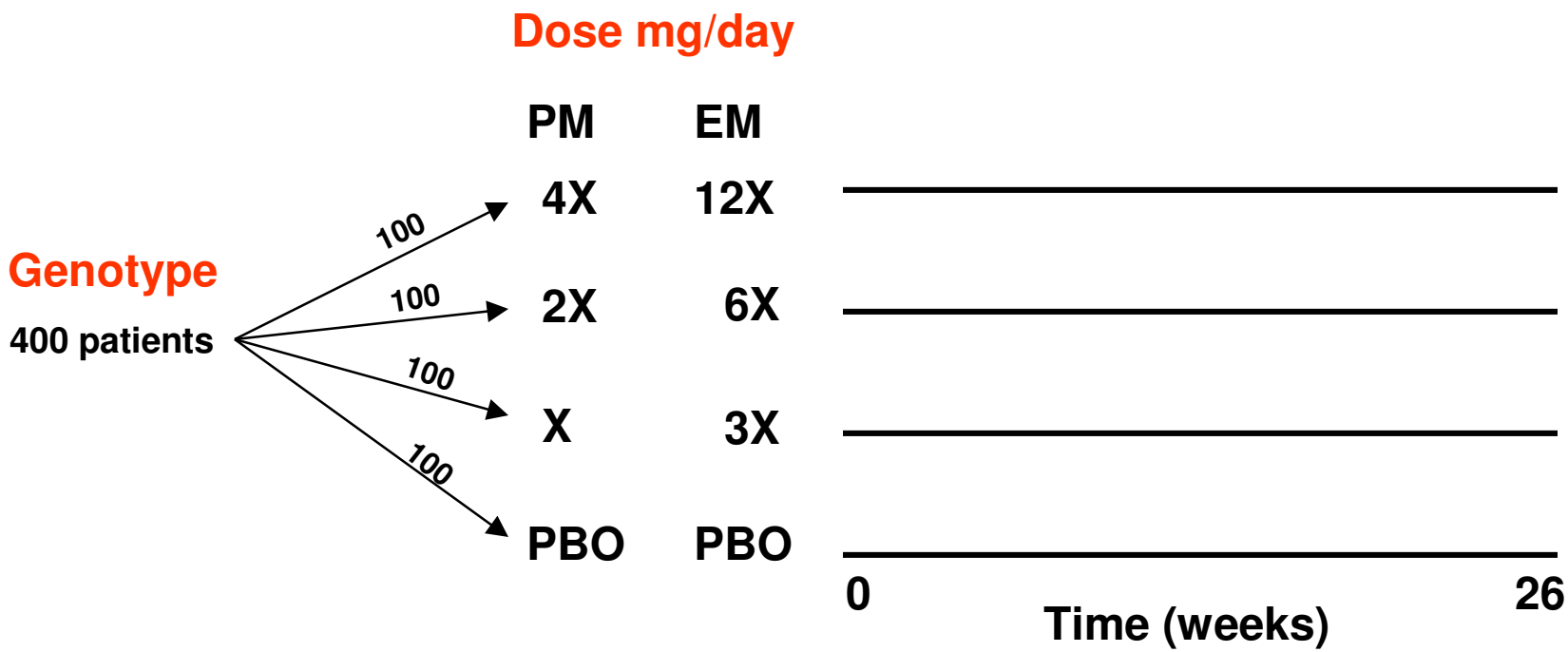
Enrichment by Genotype

(Genotype 1st, Parallel Dose, Placebo Control)

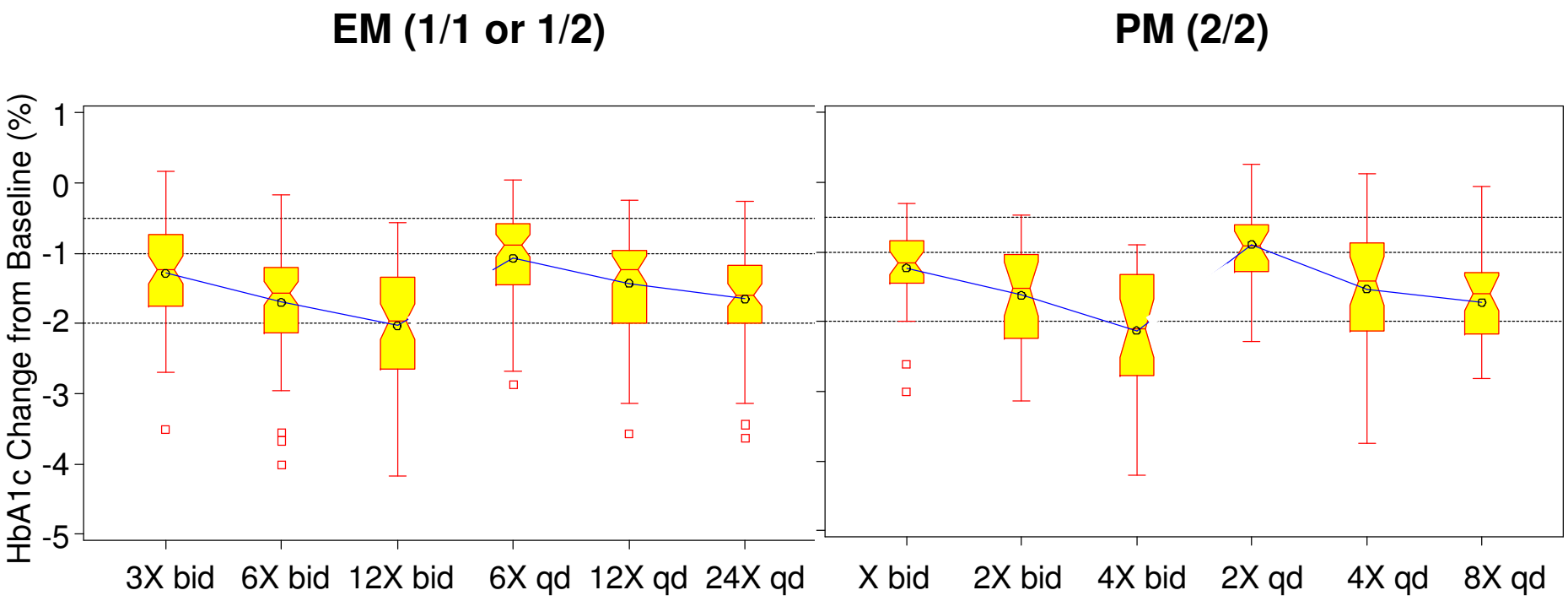
100 Patients = 27 *2/*2, 52 *1/*2, 21 *1/*1

PM

EM



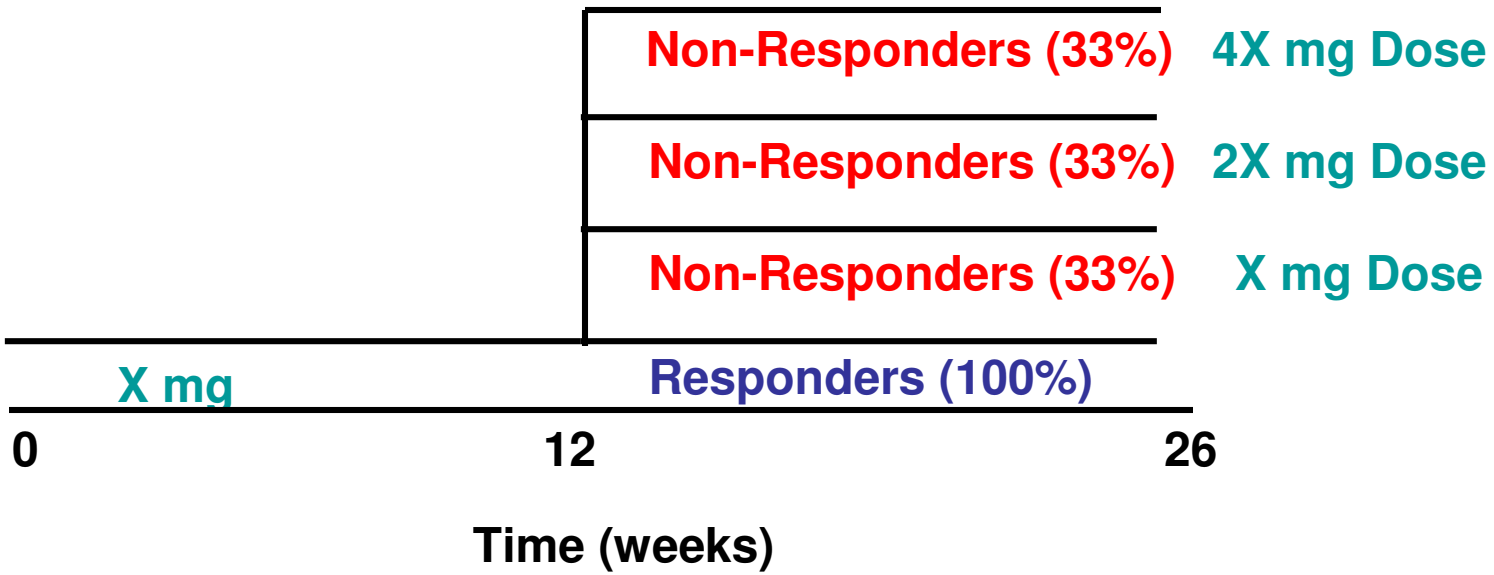
HbA1c Change from Baseline at Week 26
(naïve only, no placebo effect)



- **PM response ~ EM response @ 3X dose**
- **Dose-response evident**
- **BID better than QD**

Enrichment by Response

Randomize Low Dose Non-Responders (FPG ↓ <1.5 mmol/L) *to Med and High Doses*



% Non-responders at week 12 (FPG ↓ <1.5 mmol/L)

	Simulation	2 Sponsor trials X mg QD
*1/*1 EM	70	65
*1/*2 EM	64	68
*2/*2 PM	45	46

Recommendations & Follow-on Thoughts

- **Trial Design Strategies:**
  - a) **Enrichment by genotype: stratify into parallel dose**
    - **Dose selection: X & 2X mg daily doses for PM's are informative (naïve + experienced)**
    - **BID performs better than QD, more so in EM's**
    - **Sustained release could help**
  - b) **Enrichment by response**
    - **Further evaluation by M&S if sponsor is interested.**
- **FDA analysis sent to sponsor**

Drug-disease models at FDA

- **Primary sources**: literature, scientists, prior NDA's
- **Types**
  - Mechanistic
  - Empirical
- **Diseases** over past year
  - HIV
  - Diabetes Mellitus
  - Parkinson's Disease
  - Vasomotor Symptoms (Hot Flashes)
  - SLE-renal flare
  - Prostate Cancer- chemical castration
  - Kidney transplant rejection
- **In Development**
  - Osteoarthritis
  - Non-small cell lung cancer
- **Considering**
  - How to share models & some data on public website. Public dialogue on growing models

People

- Attributes
  - Quantitative skills (Clin PK/PD, Biostats, Engineering)
  - Clinical Judgment
  - Teamwork
  - Communication
- Training
  - New hires
  - Fellows
  - Sabbaticals

Ideal Pharmacometrics Training Location

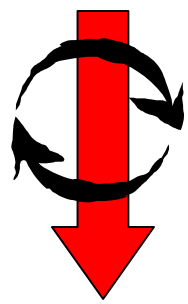
300+ Companies
INDs & NDAs

'expresso'

Measure

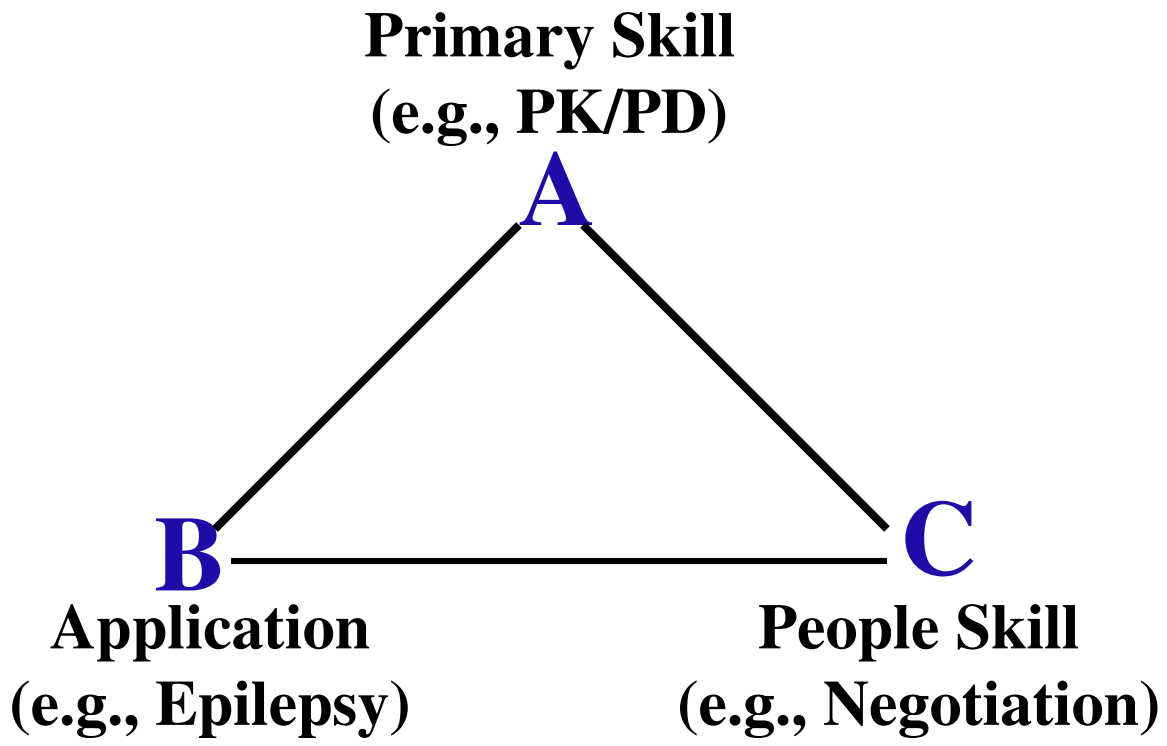
- **Disease change**
- **Safety change**
- **Dose-response**
- **Personalize**

Short cycle time



Answers count: High Impact

Personal Impact Triangle



Skill		High		Low
A-B	→	Knowledge, Judgment	→	Effectiveness
A-C	→	Influence	→	Judgment
A-B-C	→	Wisdom, Influence, Effectiveness, Impact		

Closing Thoughts

- **Technology & Leadership drive opportunity**
- **Dose-response still important source of drug development failure & toxicity once drugs are on market**
- **These problems are real, not abstract & provide a great mission for a career**
- **Impact is education & more**