Impact at a glance

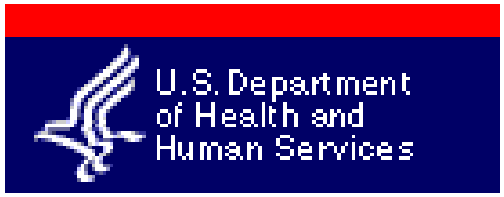
Drug	Impact	Reviewer(s)
Risperidal	Drug-drug interactions in label	Sekar, Uppoor
Minoxidil	Risk assessment to support approval	Fadiran et al
Sotalol	Pediatric dosing based on biomarkers	Gobburu, Marroum
Pain drug	Supportive evidence	Sun, Doddapaneni

Impact at a glance

Drug	Impact	Reviewer(s)
Trileptal	Monotherapy in pediatrics without controlled clinical trials	Sekar, Duan, Uppoor
CCB	“Approvable” due to sub-optimal dosing regimen	Beasley, Marroum
Zometa	Dose adjustment in renal impaired	Ramchandani, Booth, Rahman
Busulfan	Pediatric dosing	Booth, Rahman

Impact at a glance

Drug	Impact	Reviewer(s)
Varenicline	Dose-response to support lower doses in labeling	Zheng, Srikanth, Doddapaneni
Ranolazine	supportive evidence; Contraindication of hepatic impaired	Beasley, Bhattaram, Marroum
PAH drug	Cause of trials failure; alleviation of false +ve QT signal	Wang, Beasley, Marroum
CNS drug	Confirmatory evidence	Yasuda, Uppoor



Non-exclusive list

Acknowledgements

- All OCP reviewers, past and present, who contributed to the many pharmacometrics reviews and without whose excellent work I will not be here

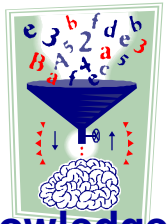
  - **Special thanks to our Pharmacometrics team!**

- OCPB Team Leaders who contributed to the survey and reviews

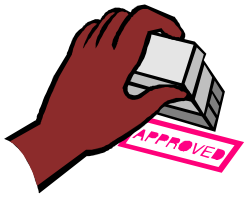
Evolution of Pharmacometrics at FDA: More IND/NDA Opportunities and Greater Demand from Medical

Decisions

Disease Models



Knowledge



Design

Policy

1992-2000	2000-2004	2005-2010

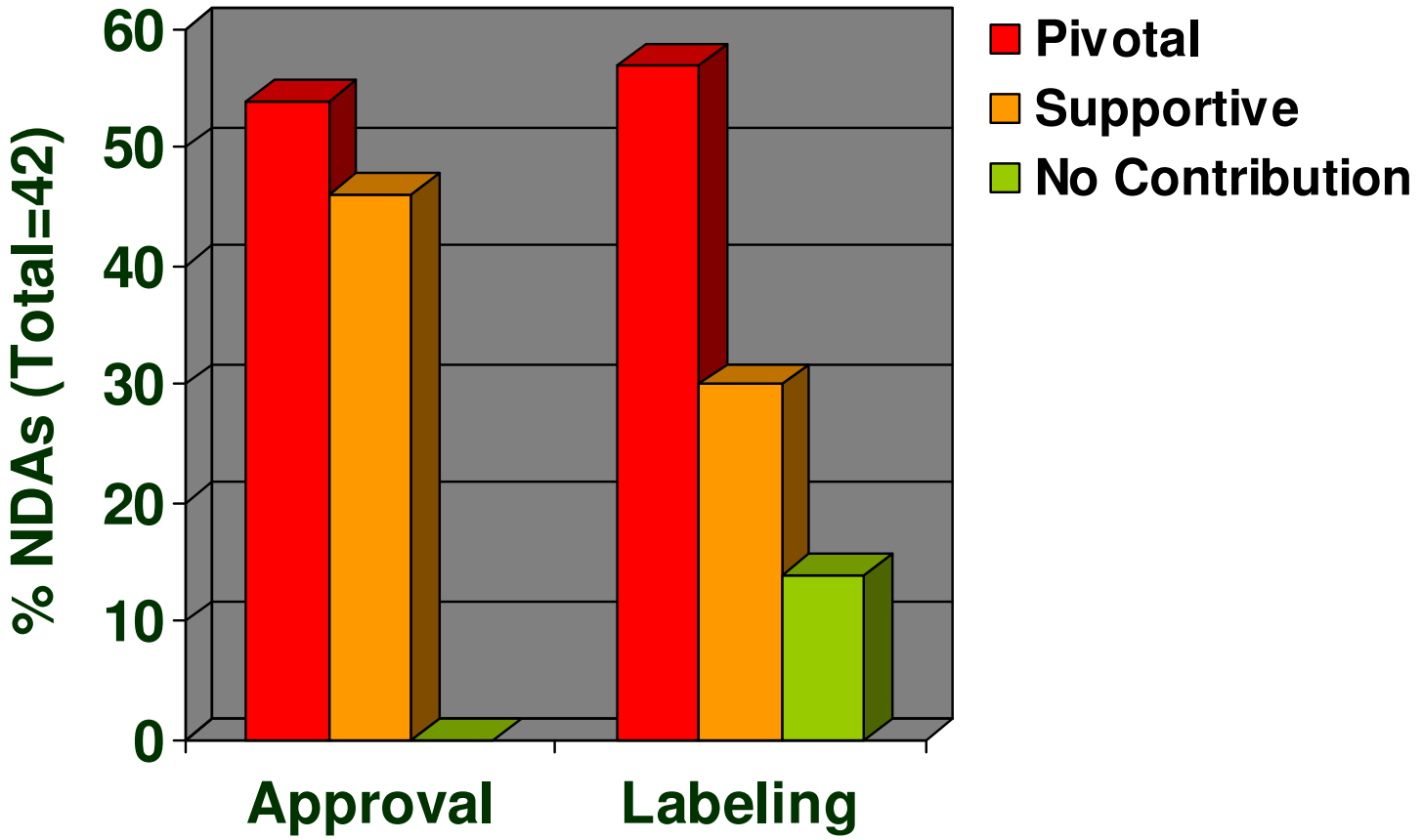
The aaps Journal

Impact of Pharmcometrics on Drug Approval and Labeling Decisions: A Survey of 42 NDAs

Venkatesh A. Bhattaram, Brian P. Booth, Roshni P. Ramchandani, B. Nhi Beasley, Yaning Wang, Veneeta Tandon, John Z. Duan, Raman K. Baweja, Patrick J. Marroum, Ramana S. Uppoor, Nam Atiqur Rahman, Chandrahas G. Sahajwalla, J. Robert Powell, Mehul U. Mehta, Jogarao V. S. Gobburu

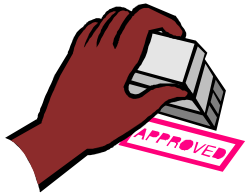
***AAPS Journal*. 2005; 7(3): Article 51. DOI: 10.1208/aapsj070351**

FDA Pharmacometrics reviews pivotally impacted approval and labeling



Case Study#1

FDA's proactive model-based analysis alleviated the need to conduct additional clinical trial for the approval of Trileptal monotherapy in pediatrics



Reviewers

Drs. Sekar, Duan, Uppoor, Gobburu

Regulatory Issue

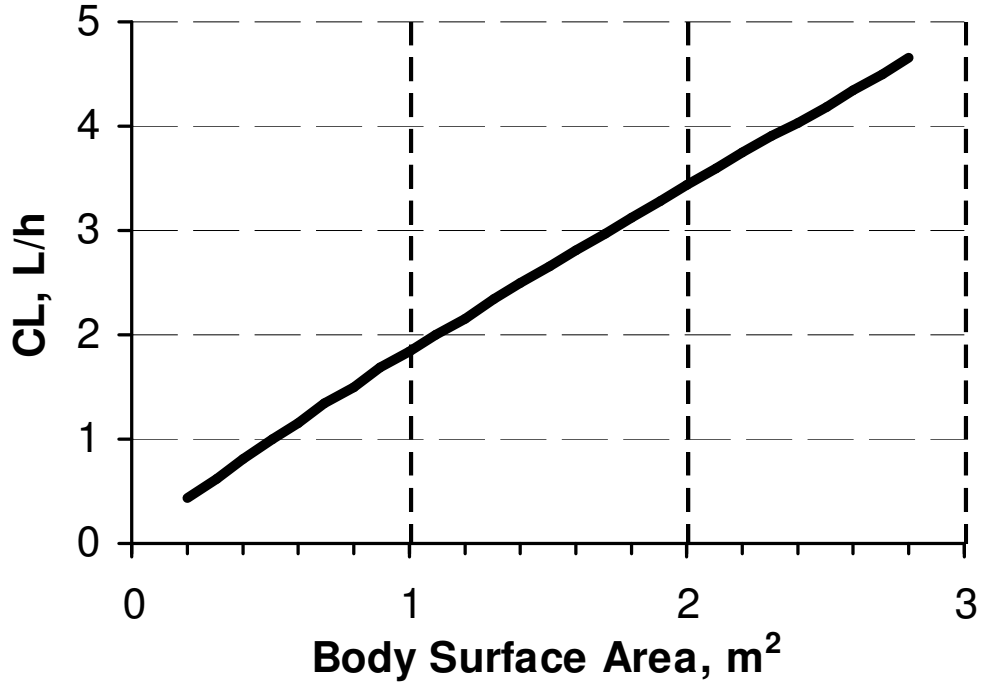
	Adjunctive	Monotherapy
Adults	Clinical trials	Clinical trials
Children (4-16 years of age)	Clinical trial	"Model Based Bridging" approach proposed by FDA

FDA/Sponsor pursued approaches to best utilize knowledge from the positive trials to assess if monotherapy in pediatrics can be approved without new controlled trials

Motivation for PM Analysis

- Monotherapy of anti-epileptics is important
  - Better safety, Ease of Rx mgmt
  - Avoid unnecessary costs
- Monotherapy trials are challenging
- Reasonable ER knowledge available
  - Integration of knowledge across trials and populations is needed
- Law supports model based thinking

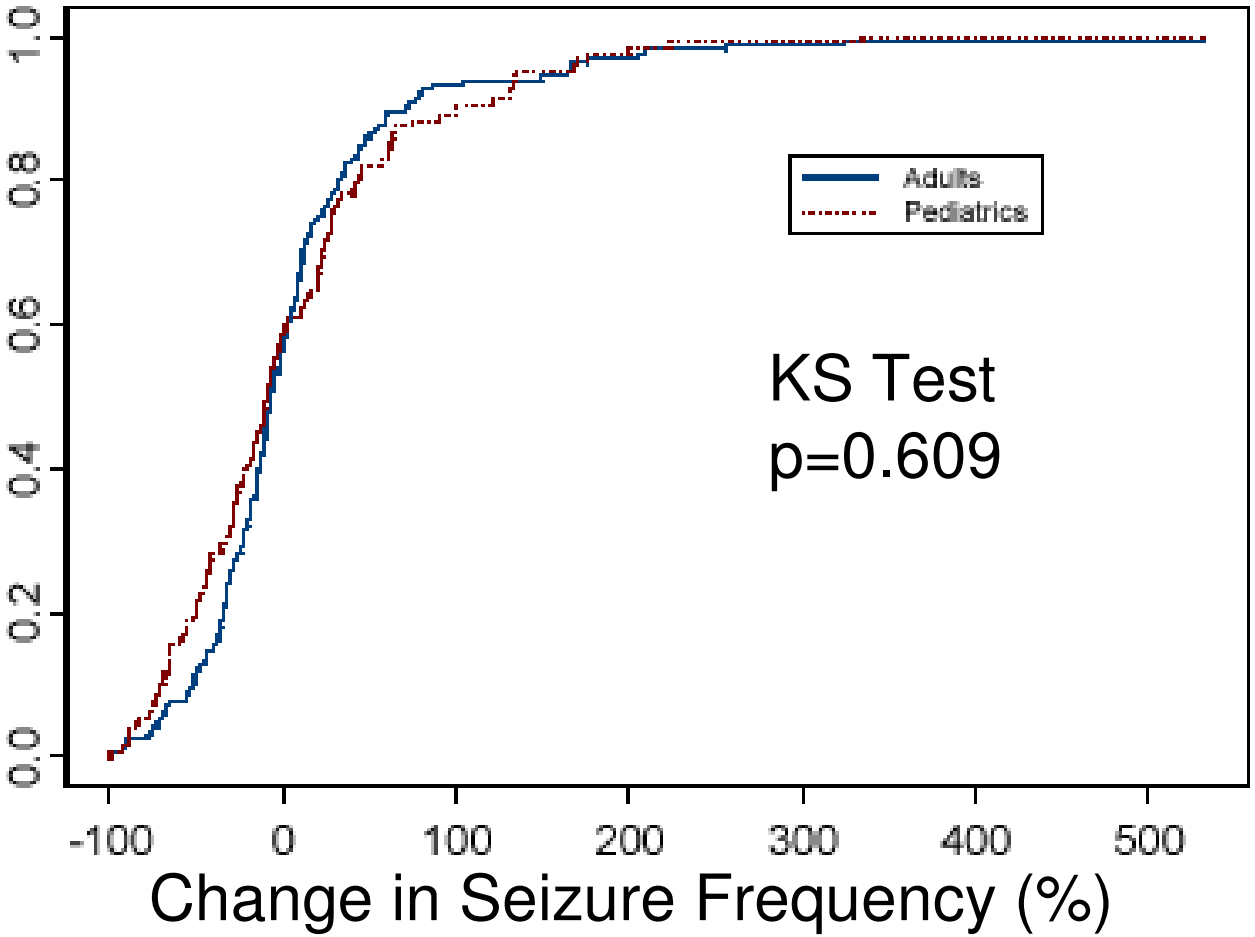
Is the exposure in pediatrics predictable from that in adults?



Population PK analysis suggested that differences in PK can be explained using body size

Simulated curve using the final PPK model

Is the placebo effect in pediatrics comparable to that in adults?



- Suggests similar response to adjunct therapy

Is the exposure-response in pediatrics comparable to that in adults?

- Significant Cmin (trough) - seizure reduction relationships exist (adjunct therapy)
- Exposure-response for adults and pediatrics are reasonably similar

Population	N	β_0 (s.e.)	β_1 (s.e.)
Adults	480	4.55 (0.04)	-0.010 (0.0011)
Peds	230	4.54 (0.06)	-0.0072 (0.0015)

β_0	*placebo-effect*
β_1	*Cmin-Seizure reduction slope*

Value of Pharmacometrics

- Modeling and simulation aided in utilizing all previous data to justify approval without additional controlled clinical trials
- Allowed selection of dosing guidelines in pediatrics
- The presented approach has a greater global impact
  - Precedent was set
- Sponsor's perspective
  - Economic implications

Application of Quantitative Tools to Efficient Decision Making: Where is FDA Going?

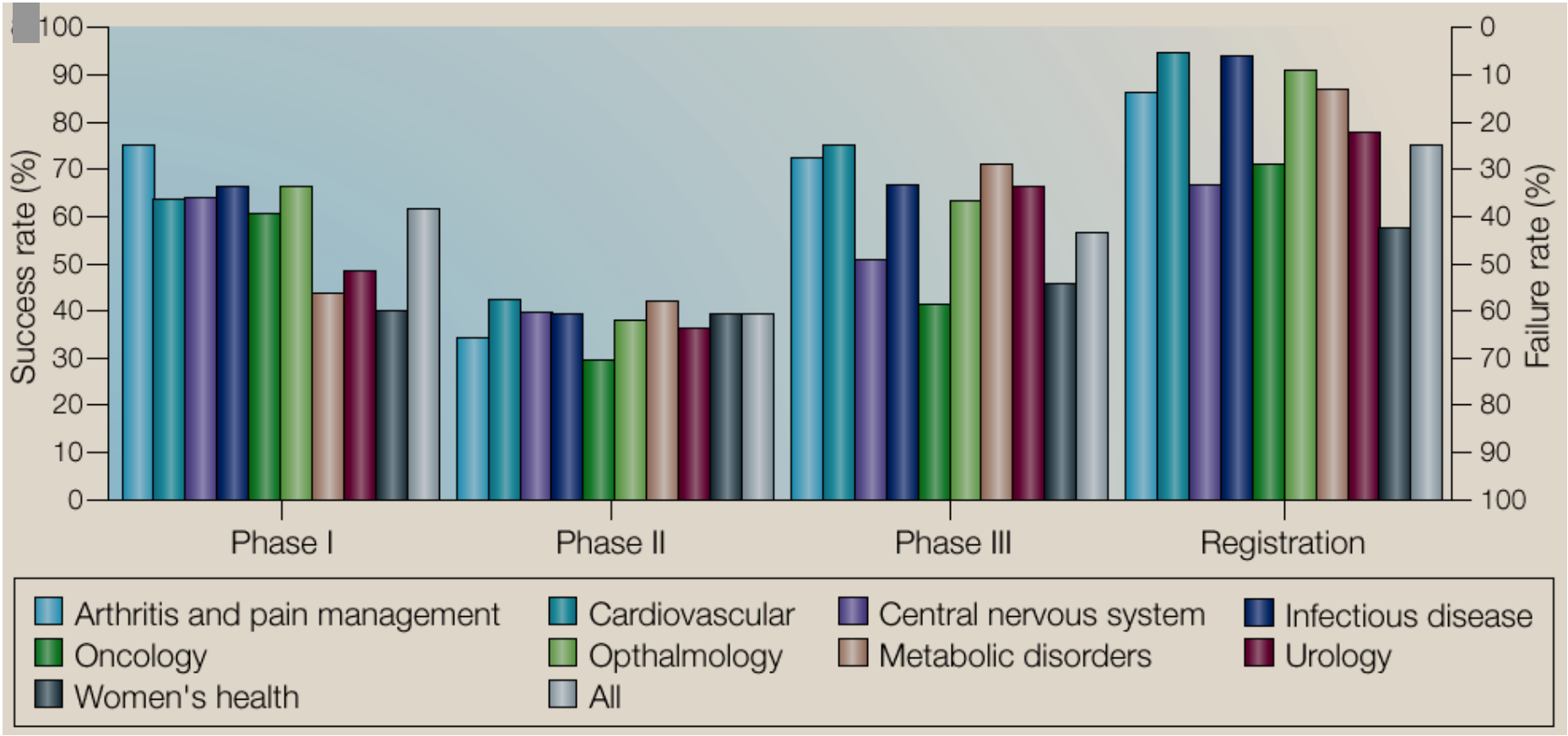
Joga Gobburu

Pharmacometrics

Office Clinical Pharmacology, Office of Translational Science (OTS), CDER, FDA

jogarao.gobburu@fda.hhs.gov

High attrition rate even in late development

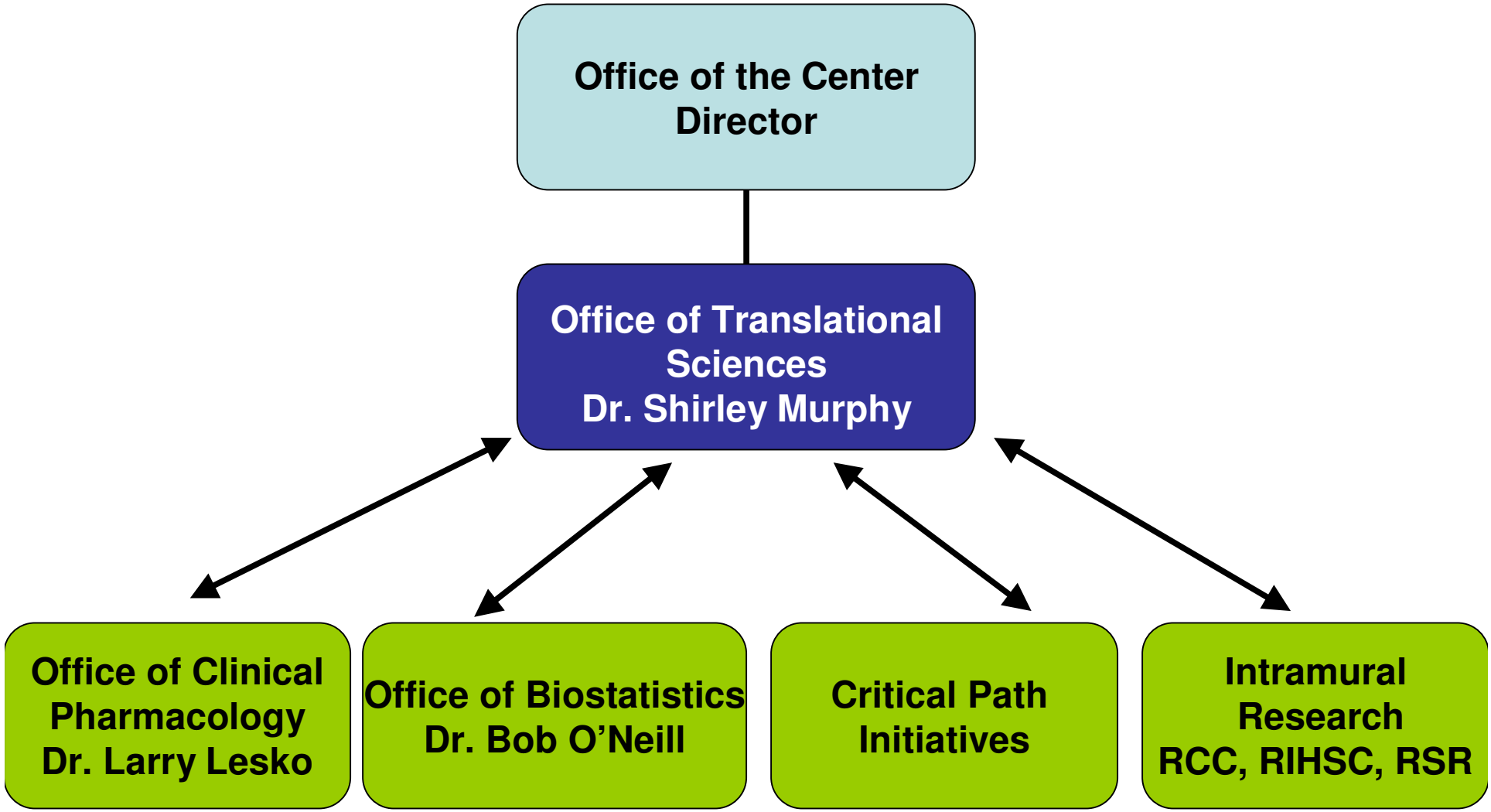


Kola I, Landis J.Can the pharmaceutical industry reduce attrition rates? ***Nat.Rev.Drug.Disc.*** *Aug 2004.*

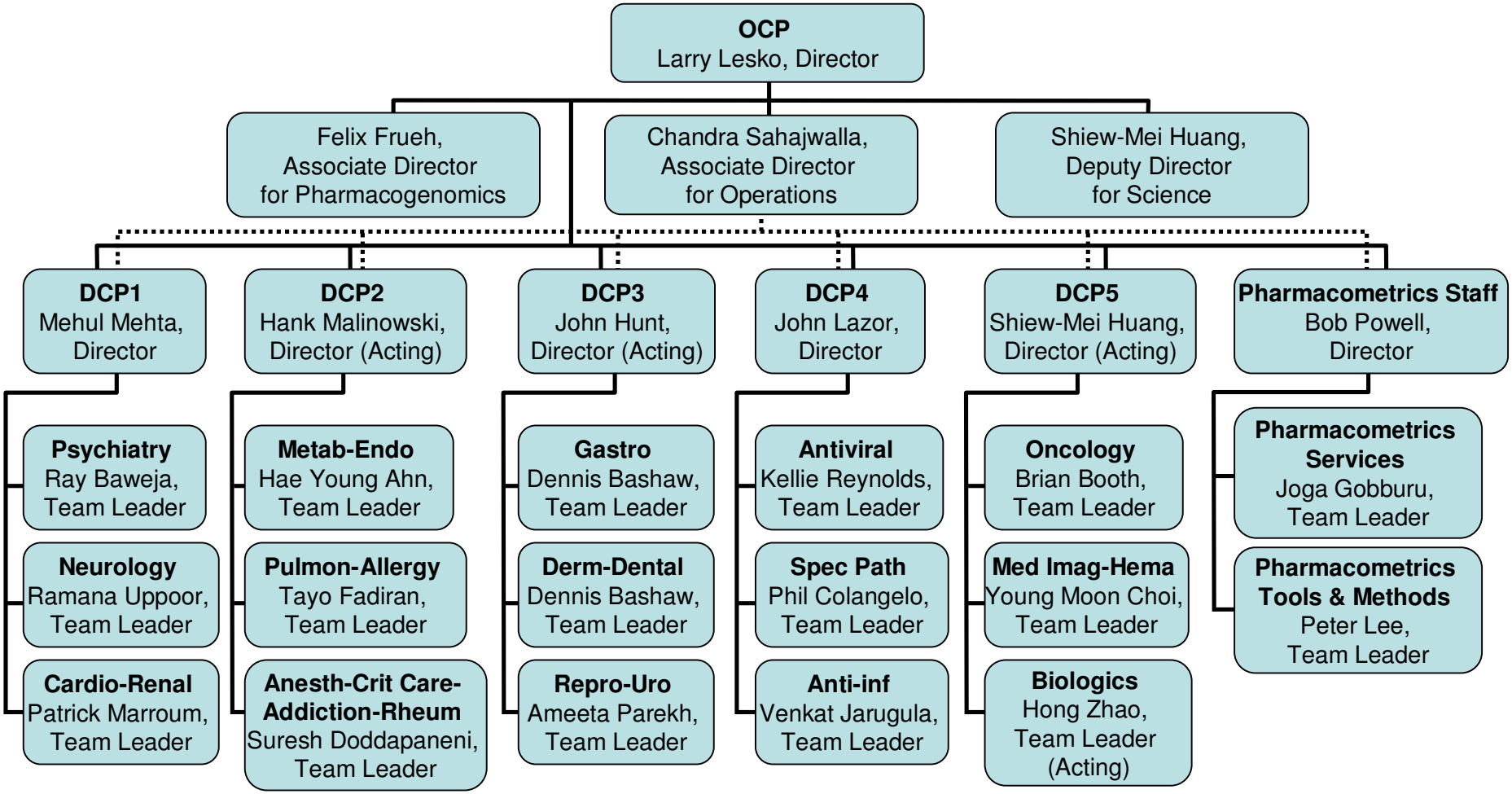
Pharmacometrics
(or Quantitative Experimental Medicine?)

- Science that deals with quantifying disease and pharmacology

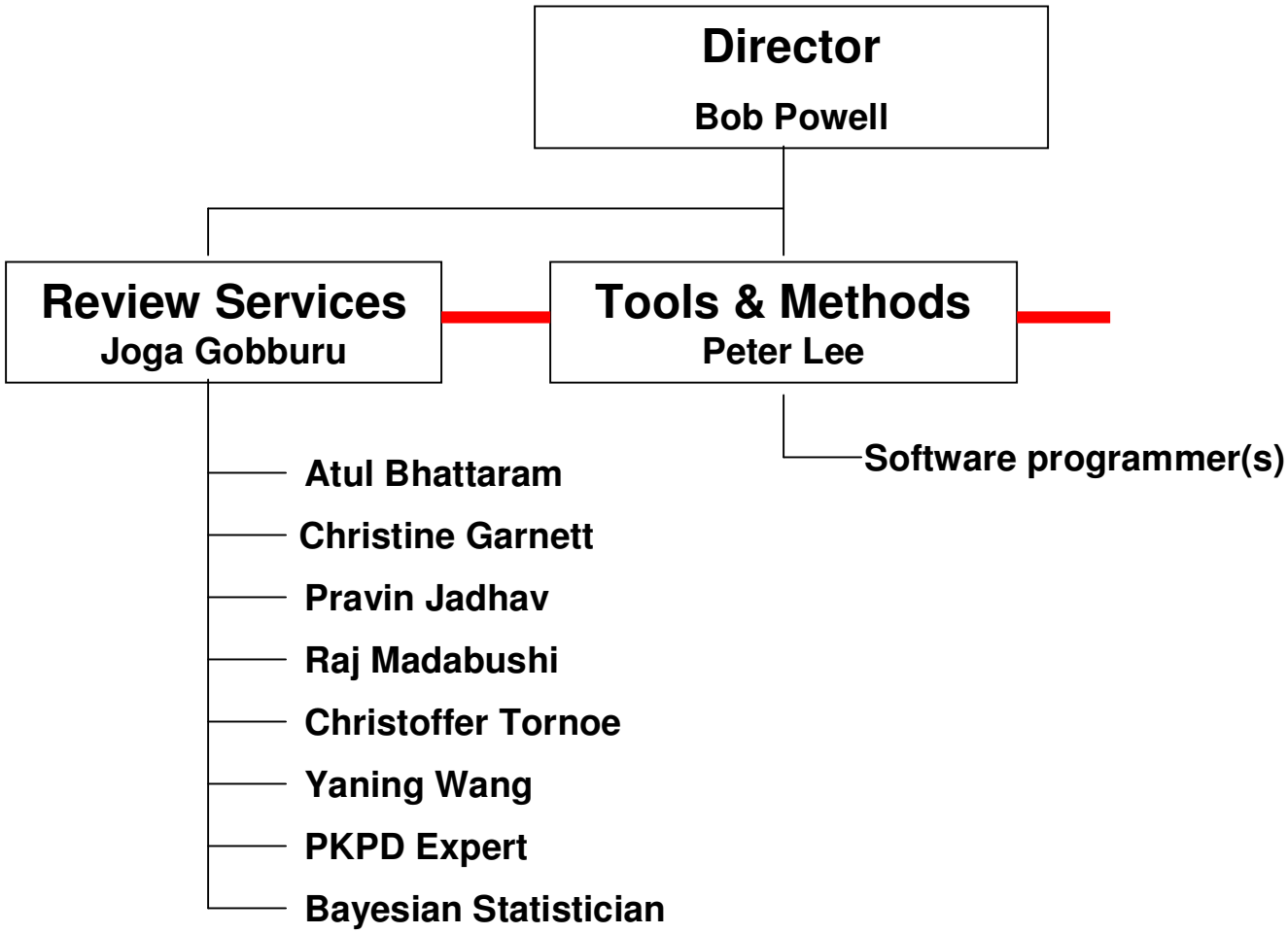
  – Single individual or diverse group?
    - Clinical pharmacologists, Pharmacometricians, Clinicians, Statisticians, Bioengineers


Office of the Center Director
Office of Translational Sciences
Dr. Shirley Murphy
Office of Clinical Pharmacology
Dr. Larry Lesko
Office of Biostatistics
Dr. Bob O'Neill
Critical Path Initiatives
Intramural Research
RCC, RIHSC, RSR

Office of Clinical Pharmacology



OCPB Pharmacometrics Organization



~10 more primary clinical pharmacology reviewers have Pharmacometrics skills.

Pharmacometrics Mission

- To improve the public health by increasing the efficiency and quality of clinical drug development with the application of model-based drug development.
- To develop quantitative model based tools to improve key drug development decisions (e.g., trial strategy & design, regulatory drug & label approval).
- To train and develop scientists who will perform this work at the FDA and elsewhere.
- To work collaboratively across therapeutic areas and disciplines to accomplish this mission.
- To both create disease models predicting patient outcome that can be shared inside and outside the FDA and establishing disease data library that can be used inside and outside FDA to promote understanding the disease process and how to measure improvement or worsening.

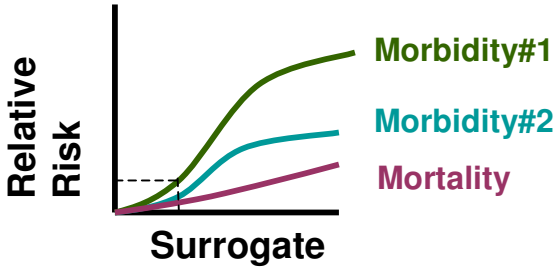
Regulatory Expectations and Opportunities for Sponsors

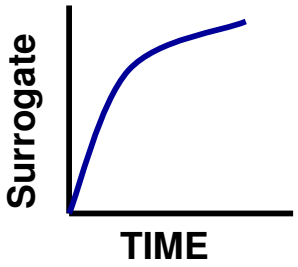
- Continued NDA Pharmacometrics reviews
  - Impact on approval/labeling decisions
- Advice on drug development strategy, trial design
  - Enhance FDA-Sponsor interactions
  - Involve quantitative thinking early-on
    - Disease models to optimize development plans
  - Critical Path Initiatives
    - Sponsors responding to FDA's call

Advice on drug development strategy and trial design: Prerequisites

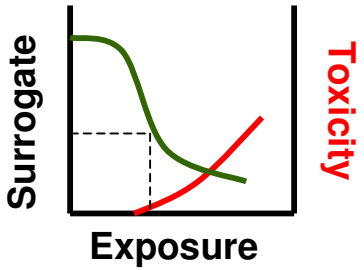
- Leverage prior knowledge
  - Disease models
- Efficient tools
- Build inter-disciplinary expertise
- Integrate pharmacometrics into decision making

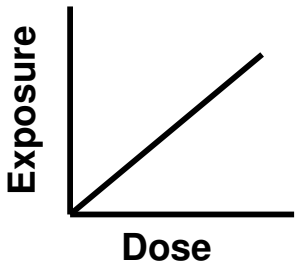
PLACEBO/DISEASE MODEL





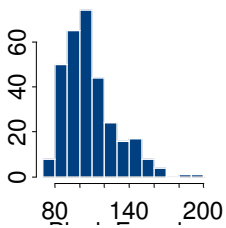
DRUG MODEL

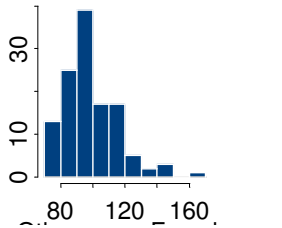




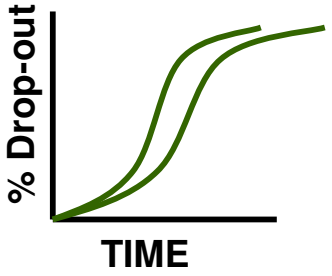
Disease Drug Trial Models

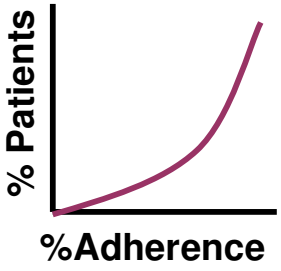
CLINICAL TRIAL MODEL



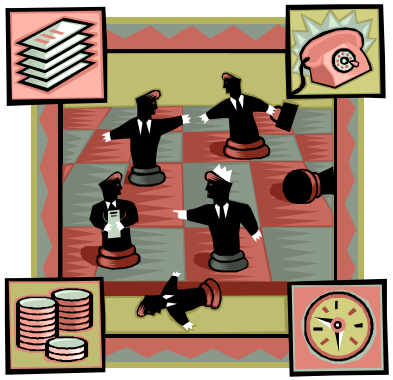


Patient Population

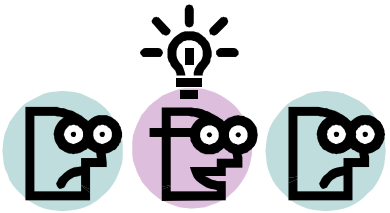




Value of Disease Drug Trial Models

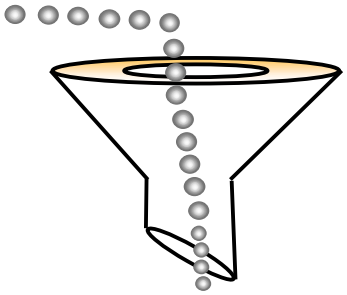


Core Development Strategy



Individualization

Approval Criteria



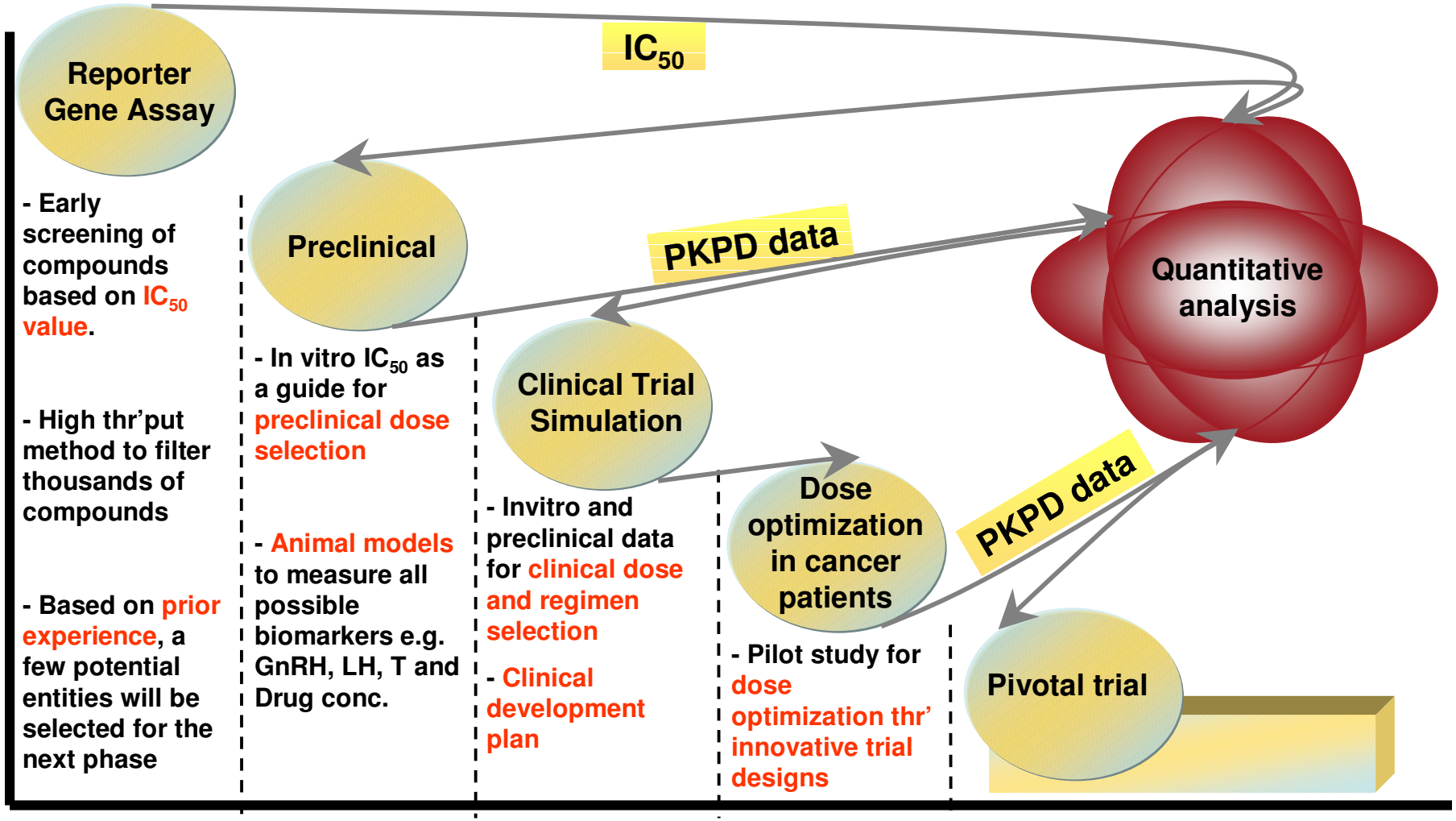
Molecule Screening

Patient Population

Dose Selection

Design

Core Development Strategy for Testosterone Suppressants



*Actual execution time.- it does account for time spent accumulating resources.

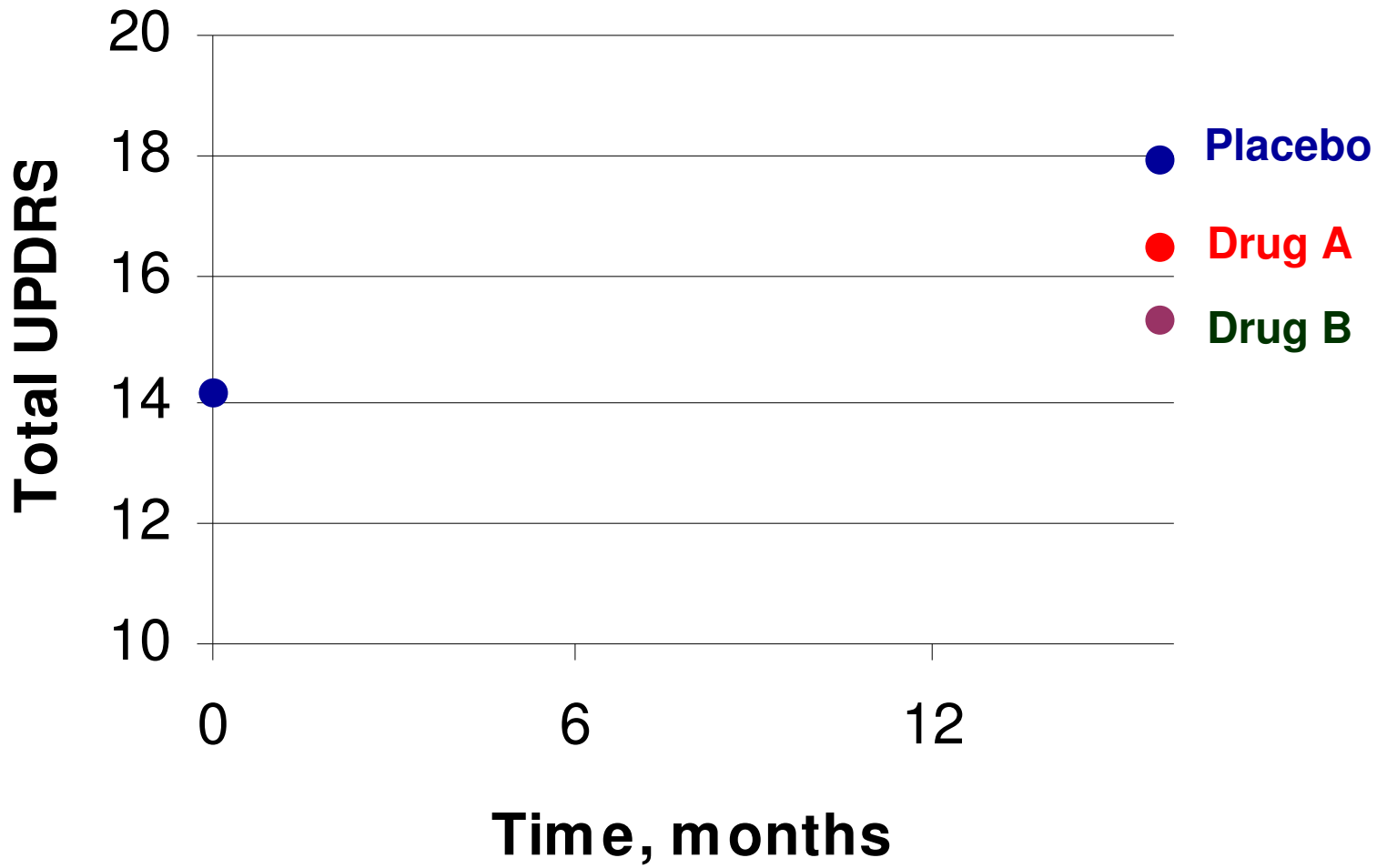
From Pravin Jadhav, VCU/FDA

Parkinson's Disease Model
Key Questions

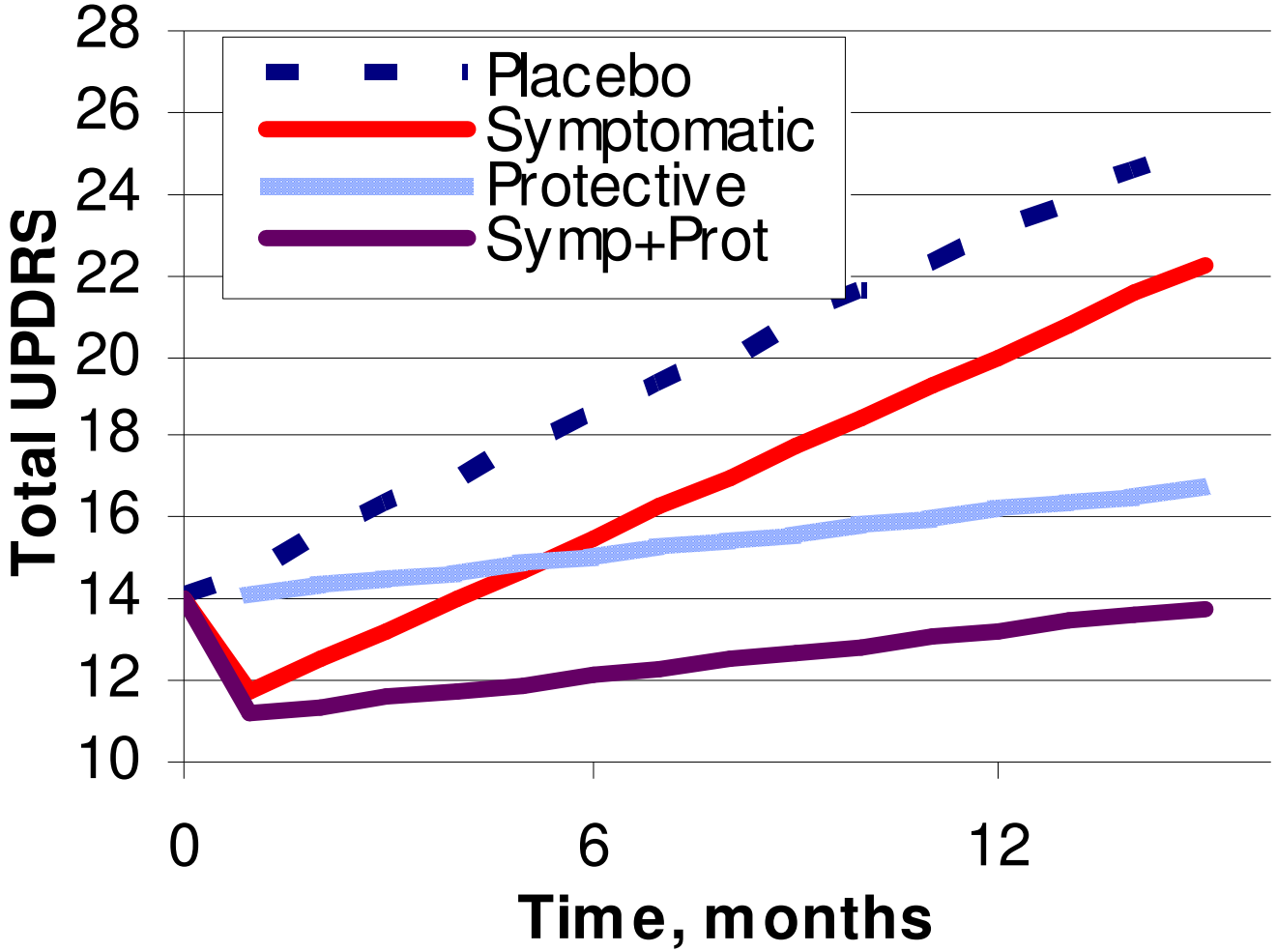
- How do we discern symptomatic vs disease modifying benefit in clinical trials?

- What is an acceptable primary analysis for approval?
  - Influence of different drug effects, drop-out mechanisms, endpoints and analysis methods

Symptomatic or Protective?



Symptomatic or Protective?



Parkinson's Disease

Dr. Bhattaram and Siddiqui are the project leads:

FDA

Statistics, Clinical, Policy Makers

External

Statistician, Disease experts

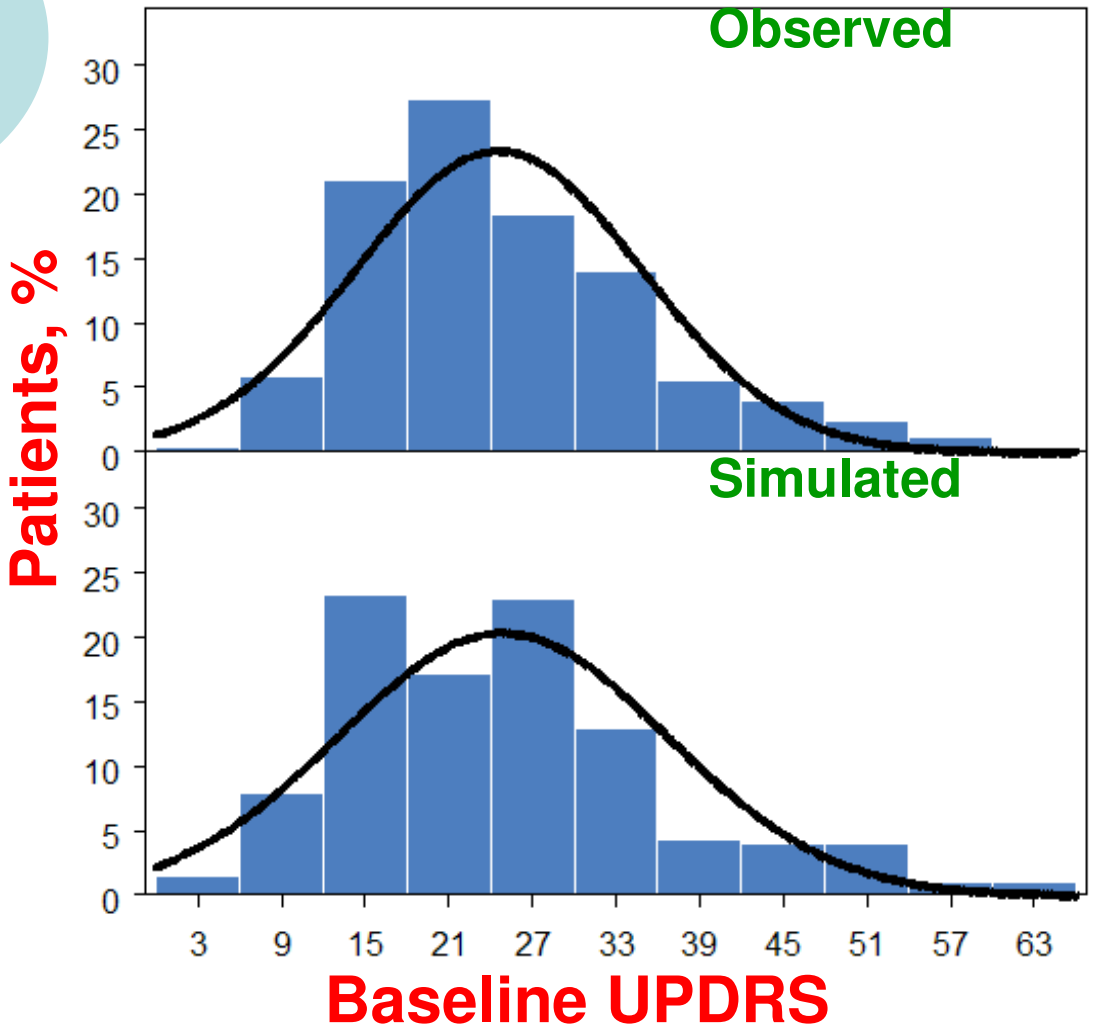
Parkinson's Disease

Collect data

Data	Source	#Patients	Trial Duration
Trial#1	NDA	400	1yr+follow-up
Trial#2	NIH	400	1yr+follow-up
Trial#3	NDA	900	9mo+follow-up
Trial#4	NDA	200	9mo+follow-up

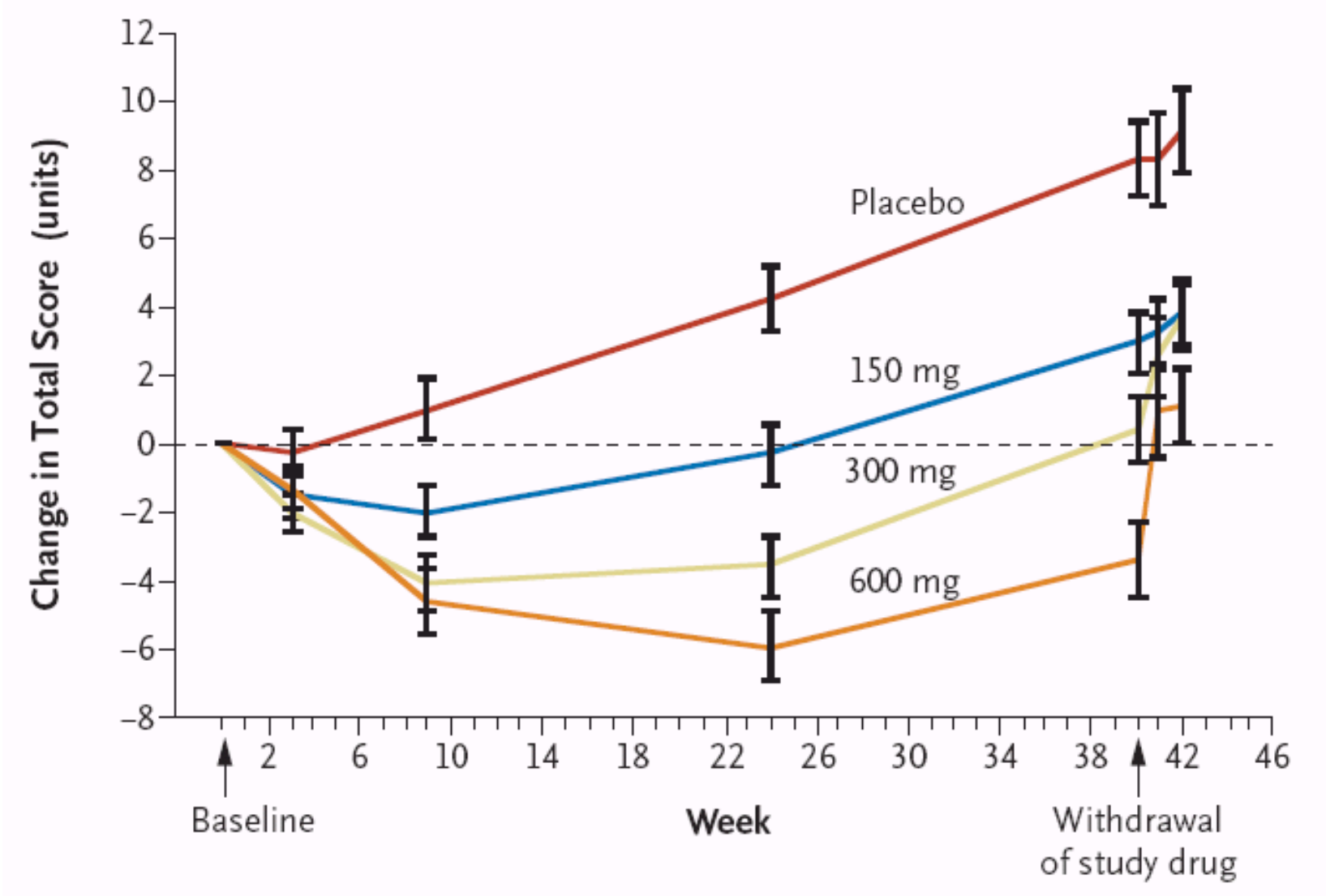
Patient Population Model

Develop
Disease
Drug
Trial
Models



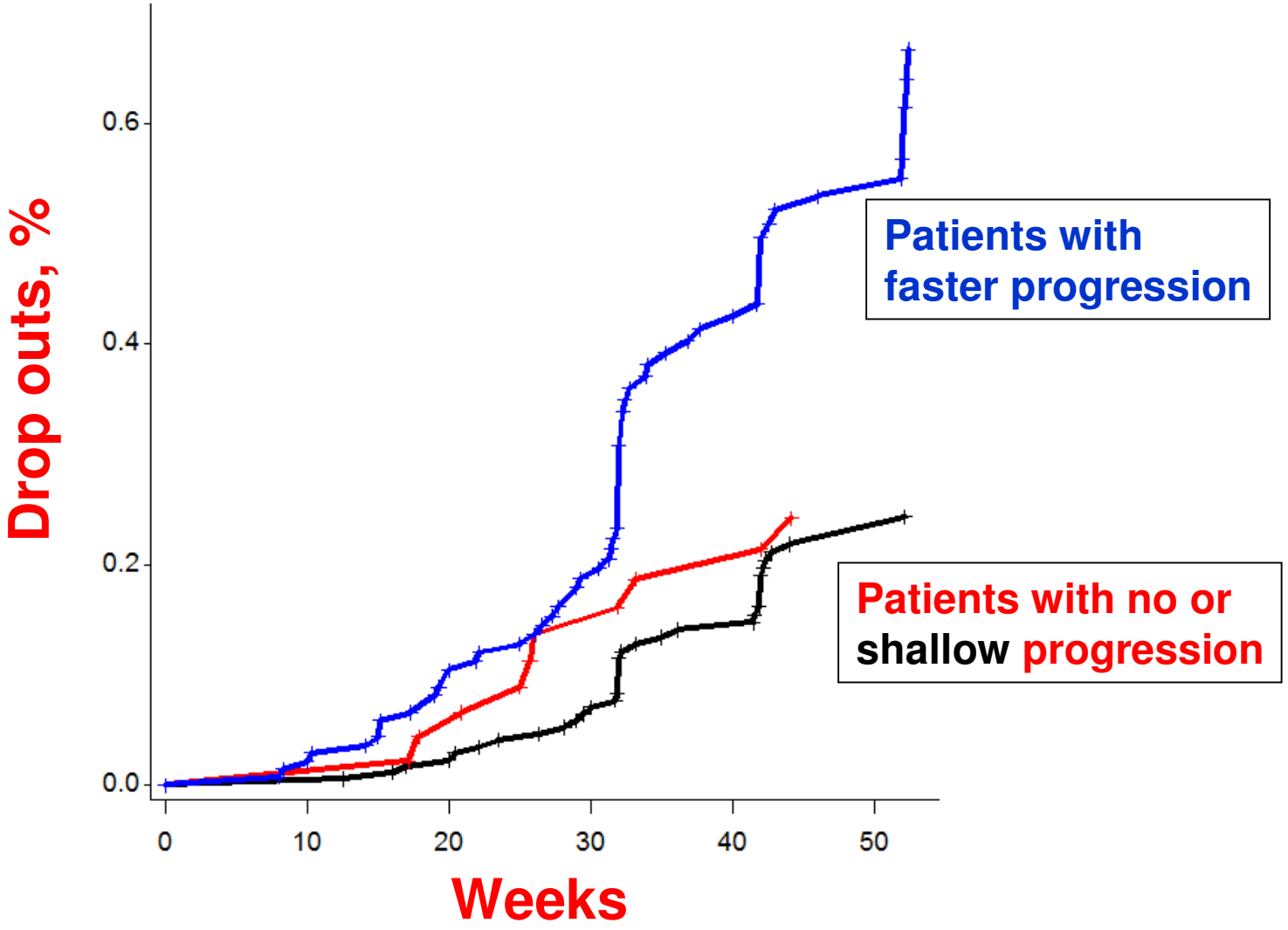
PASS

Disease Progression

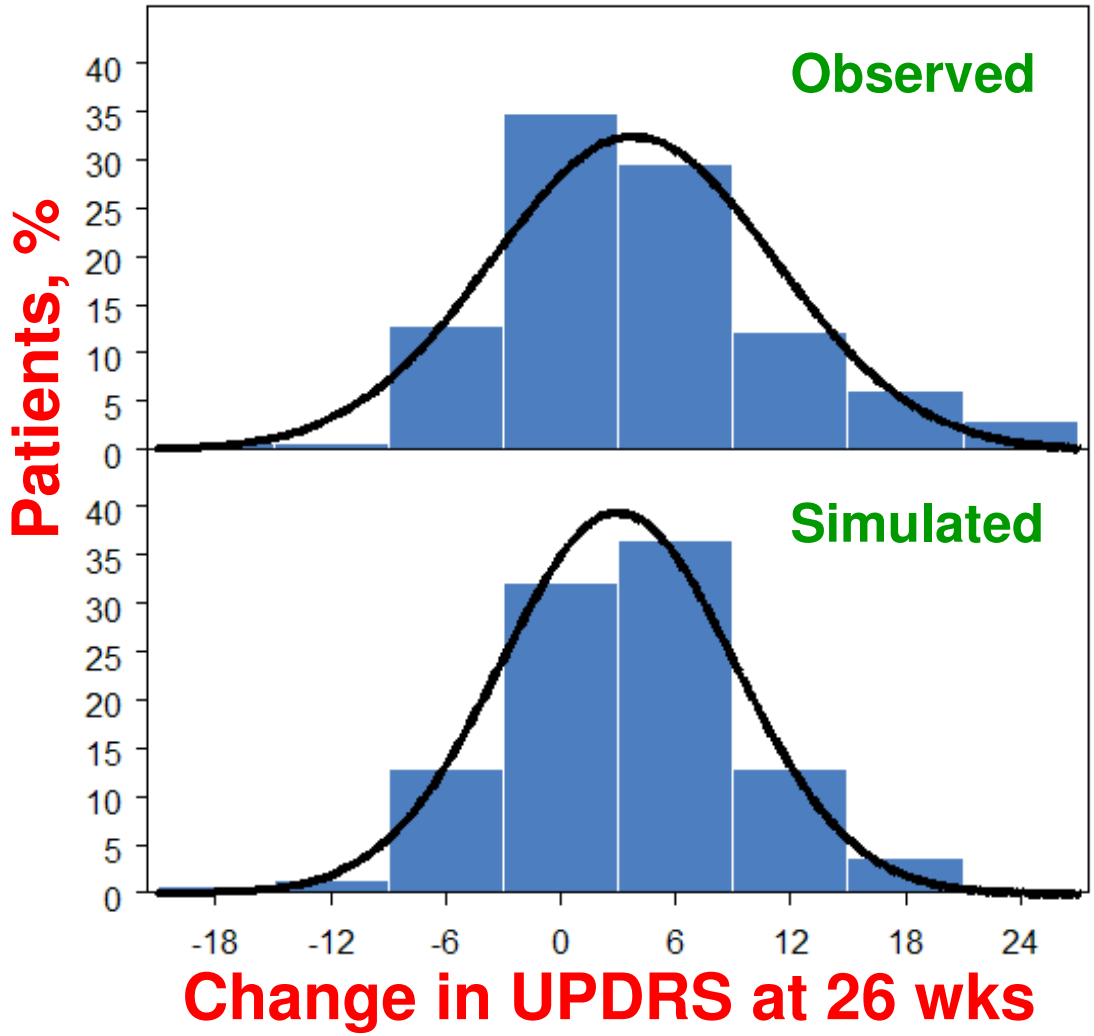


NEJM, 351, Vol 24, 2498-2508

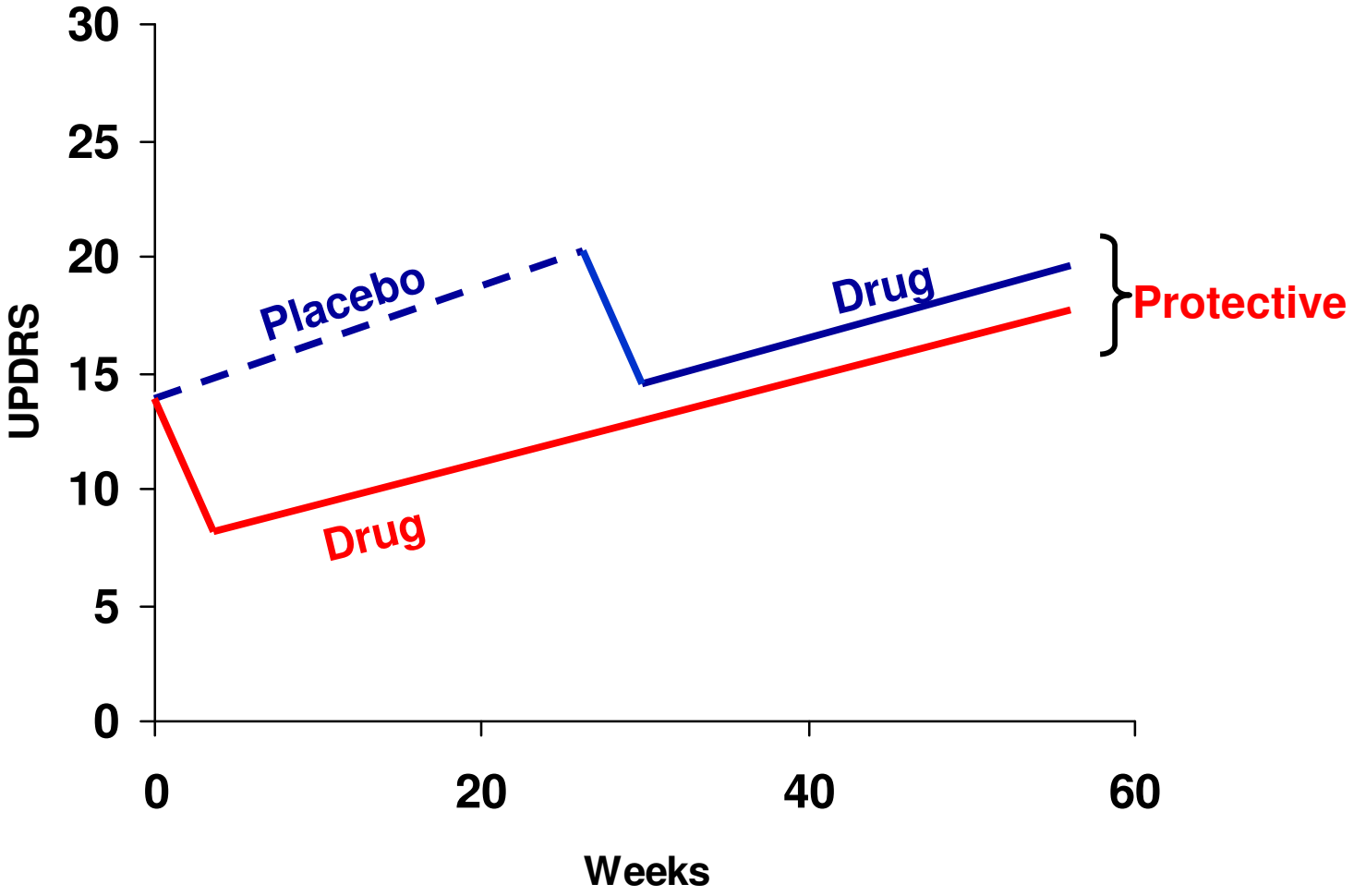
Drop-out Model



Model Qualification



Discern Symptomatic vs. Protective Effects: Delayed Start Design



If drug is protective then patients who received drug longer will have lower scores compared those who receive drug late.

False Positive Rate

Dropout Scenario	Placebo Phase	Active Phase				
		Available cases	LOCF	Group Mean	Group Max	Baseline CarryForward
MCAR	5.20	5.00	5.80	11.75	18.20	4.95
MAR (Lack of benefit; equal drop-outs)	5.15	16.35	22.60	30.70	24.70	13.20
MAR (Lack of benefit; unequal drop-outs)	4.95	7.55	11.50	11.25	22.55	6.45
MAR (Lack of benefit+Toxicity)	4.70	12.25	29.15	38.80	65.10	67.65
MNAR	-					

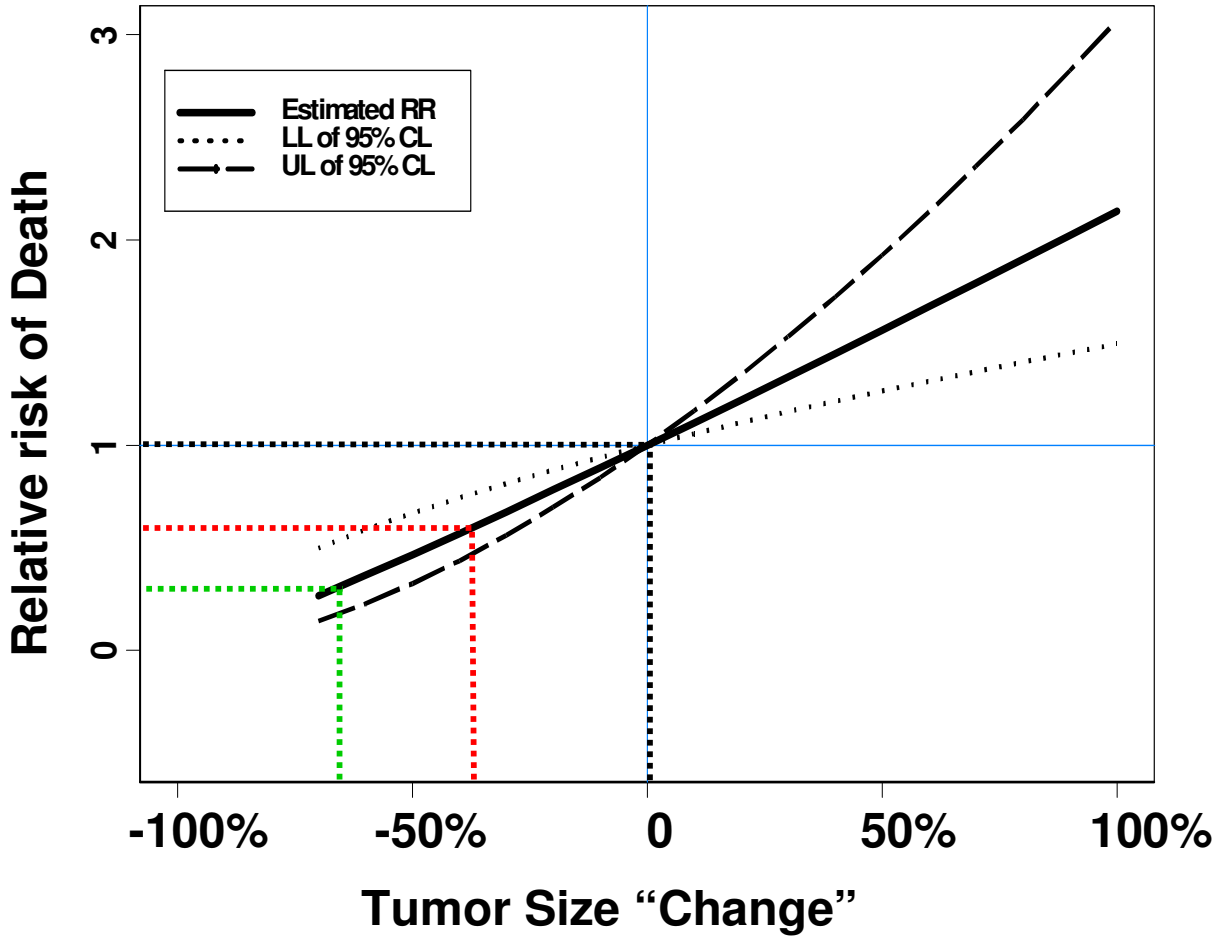
BOCF: Baseline observation carried forward
LOCF: Last observation carried forward

Parkinson's Disease Model

- Collected a large database of clinical trials
- Extracted patient population, placebo/disease progression, drug effect (not shown) and drop-out information.
- Simulations to answer the key questions mentioned earlier are in progress
- These findings will be published soon and technical details will be presented publicly soon.

Biomarker-Survival Relationship is Valuable for Efficient Drug Development

An inter-disciplinary team at FDA is developing a tumor size-survival relationship for Non-small lung cancer

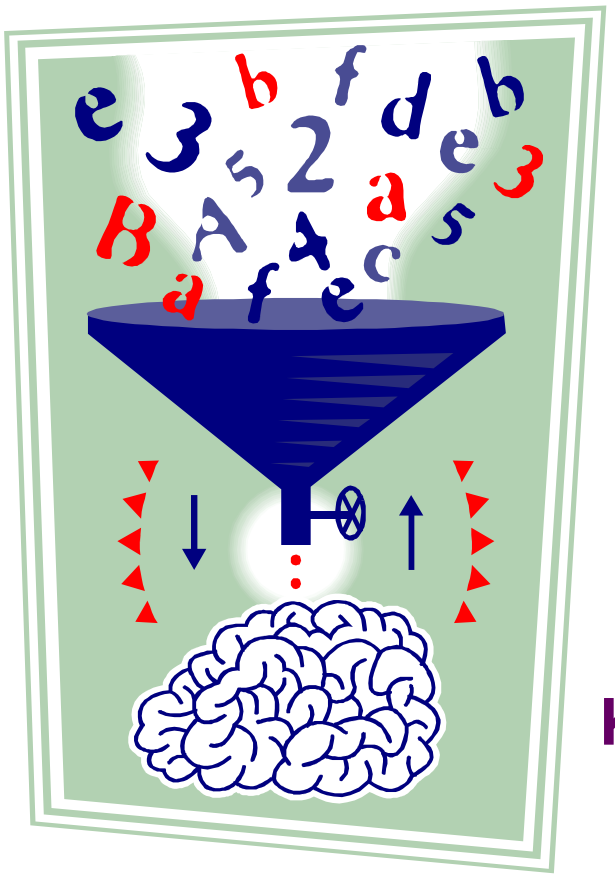


- **Screening for drugs**
- **Dose selection**
- **Verification of endpoints**

- **FDA will be in a position to guide sponsors early in drug development**

Dartois C, Sung C, Wang Y, Ramchandani R, Rock E, Booth B, Gobburu J.

Manage Knowledge



Information

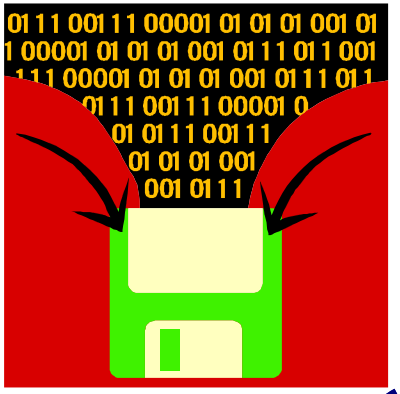
Placebo & Disease Models

- Biomarker-Endpoint
- Time course
- Drop-out
- Inclusion/Exclusion criteria

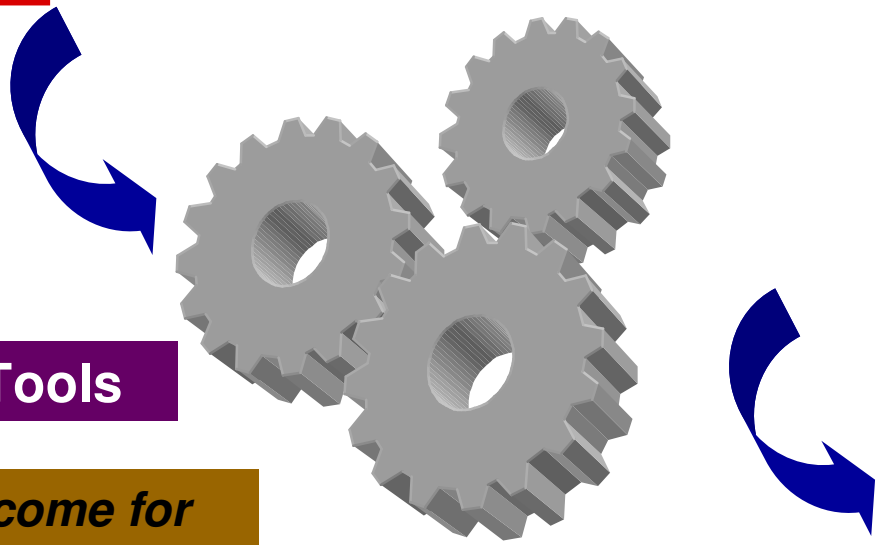
Knowledge

- Parkinson's
- Obesity, Diabetes
- Tumor-Survival
- Rheumatologic condition
- HIV
- Epilepsy
- Pain
- *Osteoporosis*

Increase Review Efficiency



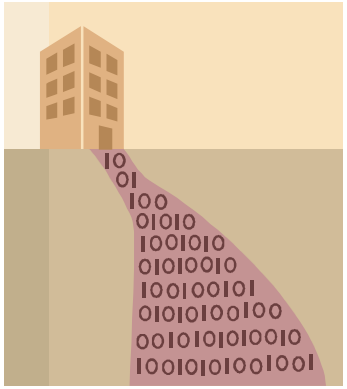
Data submission standards - CDISC



Review Tools

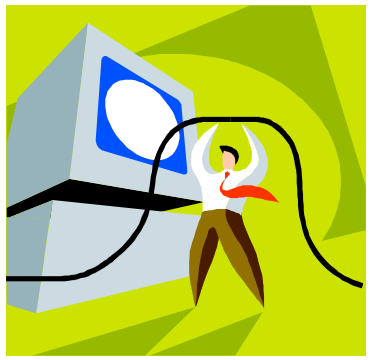
Time has come for expecting more from our software

Database

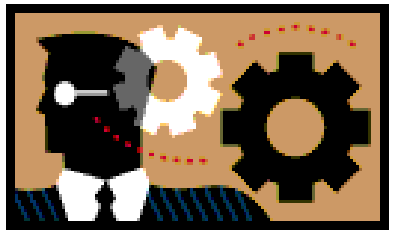


Diversify Expertise

Statistician



PKPD Expert



Clinician

Train Scientists

Increase awareness among peers

Train graduates/post-docs

- *FDA trains fellows*
- *ACCP PM website*
- *AAPS Fellowship*

PhRMA should support

Integrate pharmacometrics into mainstream drug development

- Message from FDA is loud and clear
  - Increased number of NDA/INDs with pharmacometrics analysis
  - More ‘customers’ seek consults

- Pharmacometricians need to be part of drug teams and build strategic relationships

Increase Sponsor-FDA Interaction

EOP2A meetings provide an excellent opportunity for Sponsor and FDA to exchange science on a less formal basis

We encourage Sponsors to orient the reviewers to the ClinPharm portion of the NDA

Increase Sponsor-FDA Interaction

- FDA Pharmacometrics in collaboration with Industry is planning on two meetings early 2007, focusing on:
  - Disease models
  - Pharmacometrics tools
- FDA Pharmacometrics to set up an external website – discussions ongoing

How Can Industry Help FDA Make Drug Development Process and Regulatory Review More Successful?

- Collect PK, biomarker and clinical endpoint data over range of doses in late clinical trials
- Apply quantitative methods early and continuously during IND period
- Initiate increased communication with FDA during mid/late stages (e.g., EOP2A)
- Focus on adequate identification of optimal dosing regimens in late clinical studies

Advice on drug development strategy and trial design: Prerequisites

- Leverage prior knowledge
  - Disease models
- Efficient tools
- Build inter-disciplinary expertise
- Integrate pharmacometrics into decision making

The best way to predict
the future
is to create it.

Peter Drucker