Quantitative Decision-Making in Drug Development

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Outline

- The Staggering Cost Of Drug Development
- What is Model-Based Drug Development (MBDD) and why it's needed ?
- Understanding and embracing uncertainty
- Conclusions

Cost and risk in clinical development are key drivers for change

The average drug developed by a major pharmaceutical company costs at least $4 billion, and it can be as much as $11 billion!!!

Company	No. of drugs approved	R&D Spending Per Drug ($Mil)	Total R&D Spending 1997-2011 ($Mil)
AstraZeneca	5	11,790.93	58,955
GlaxoSmithKline	10	8,170.81	81,708
Sanofi	8	7,909.26	63,274
Roche Holding AG	11	7,803.77	85,841
Pfizer Inc.	14	7,727.03	108,178
Johnson & Johnson	15	5,885.65	88,285
Eli Lilly & Co.	11	4,577.04	50,347
Abbott Laboratories	8	4,496.21	35,970
Merck & Co Inc	16	4,209.99	67,360
Bristol-Myers Squibb Co.	11	4,152.26	45,675
Novartis AG	21	3,983.13	83,646
Amgen Inc.	9	3,692.14	33,229

A key problem is separating the winners from the losers early!!!

Sources: InnoThink Center For Research In Biomedical Innovation; Thomson Reuters Fundamentals via FactSet Research Systems

Most statistical hypothesis testing in drug development is designed to answer one question at a time

Primary analysis

The following inferential null hypothesis will be tested:

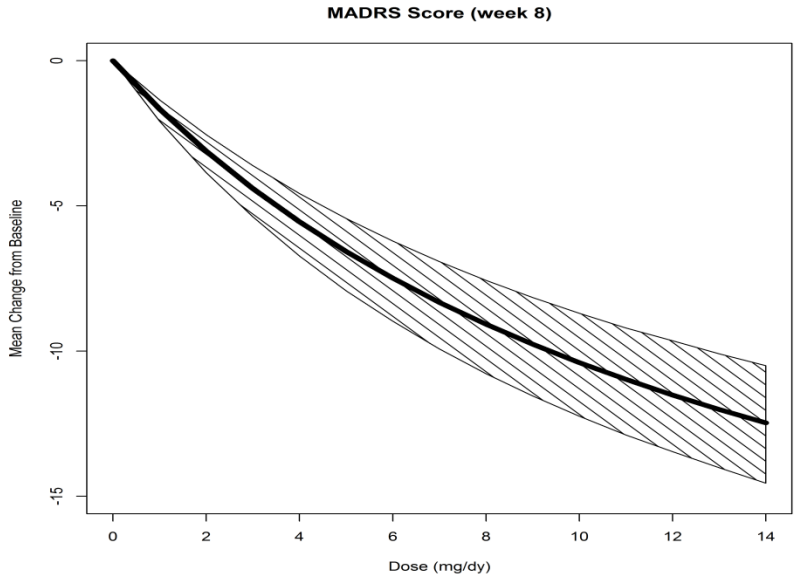
H_o : no treatment differences between 4 mg dosage group and placebo

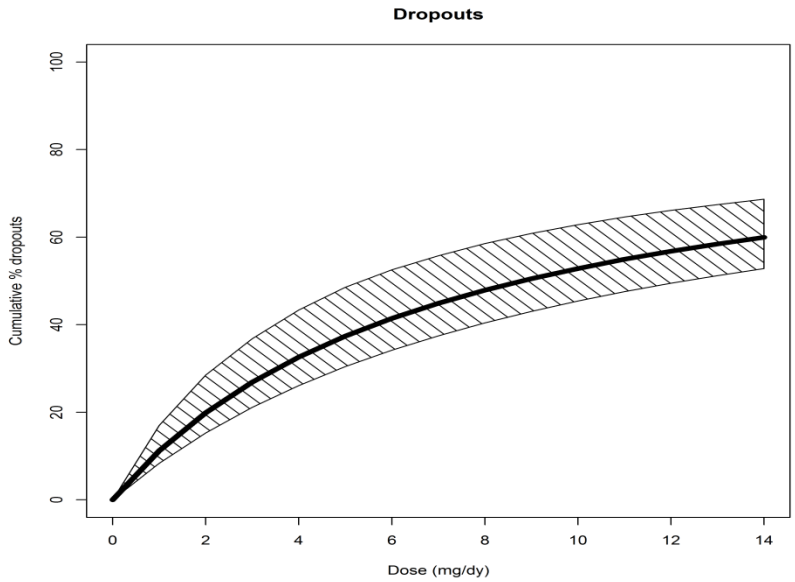
versus

H_1 : 8 mg dose group demonstrates significantly better efficacy than the placebo group

The null hypothesis Ho will be tested against the alternative H_1 two sided with $\alpha=0.05$. To preserve the alpha level at 0.05 for both the 8 mg dosage group comparison and the 4 mg dosage group comparison the critical value for the Dunnett's test for the two groups compared with a control will be used.

What dose is “best” given the trade-off of efficacy versus dropouts due to AEs?

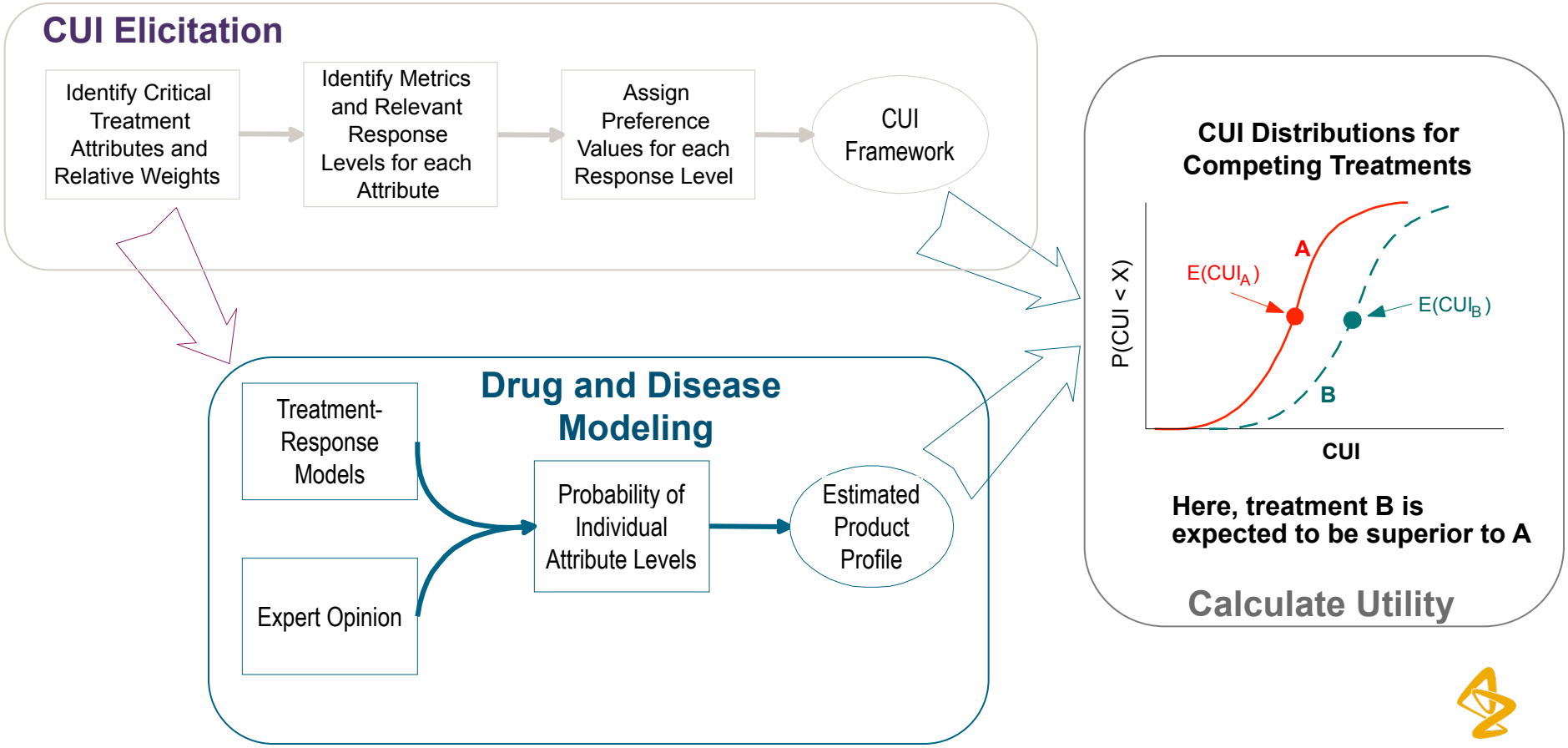




The Clinical Utility Index (CUI) quantifies these tradeoffs by providing a single metric for the multiple dimensions of benefit and risk.

The framework for the CUI may be elicited from the project team or can come from externally-derived sources

When combined with models of response, it provides an estimate of patient benefit relative to alternatives



Korsan R, Dykstra K, Pullman W. Transparent Trade-Offs: A Clinical Utility Index (CUI) Openly Evaluates a Product's Attributes and Chance of Success. Pharmaceutical Executive, March, 2005

MBDD

- FDA's categorization: the development and application of pharmaco-statistical models of drug efficacy and safety from available preclinical and available clinical data to improve drug development knowledge management and decision making.

US Food and Drug Administration. 2004. *Innovation or Stagnation: Challenge and Opportunity on the Critical Path to New Medical Products. http://www.fda.gov/oc/initiatives/*
criticalpath/whitepaper.html

The MBDD process

- Establish decision criteria (at least identify the key decision-drivers)
- Leverage prior knowledge from all available sources
  - Data on the NCE of interest
    - Preclinical, Phase I safety & biomarkers, clinical safety & efficacy …
  - Knowledge about the target disease & affected physiologic systems
  - Knowledge/data on related compounds
    - From proprietary or public sources
- Build models for all responses key to strategic decisions based on that knowledge
  - Disease progression
  - Drug models for the NCE of interest and related or potentially competing drugs
    - Efficacy-related outcomes
    - Safety-related outcomes
  - On-trial behavior, e.g., dropouts and compliance
  - Market and financial models

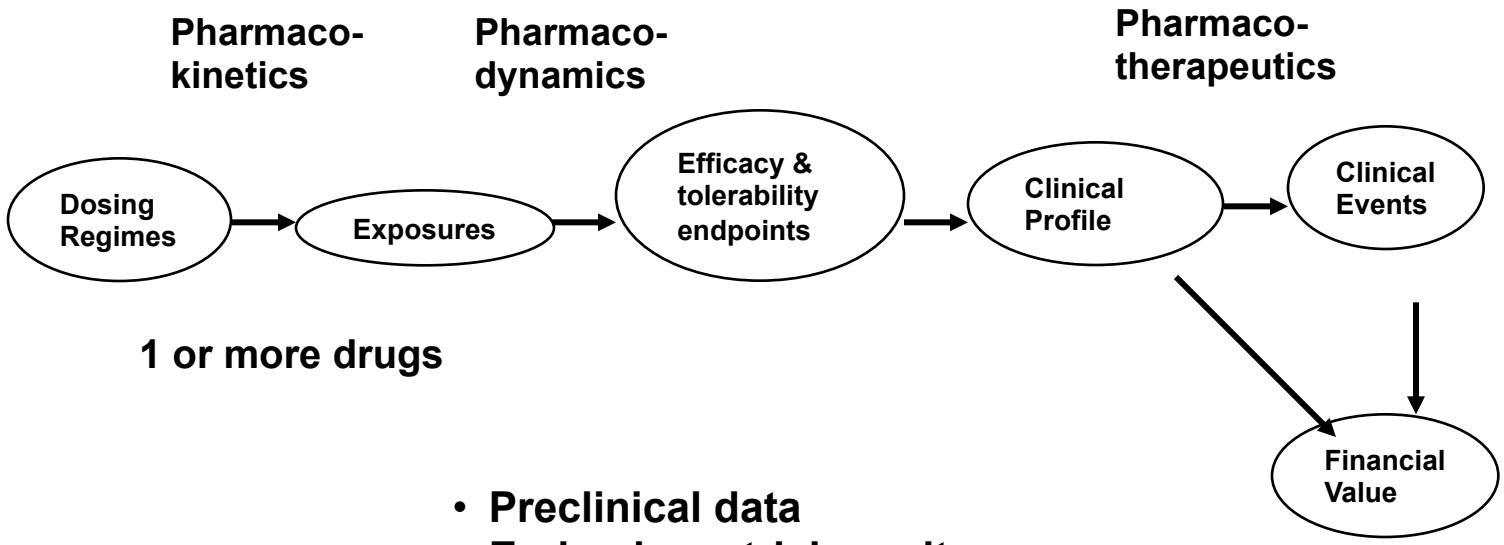
Models provide rational framework for integration and organization of disparate compound/biologic knowledge

- Model-based drug development
  - An integrated, data-driven, model-based decision-making methodology
  - Integrate all relevant public and proprietary data spanning:
    - discovery to clinical
    - in-house data to competitors' information
    - healthy volunteers to patients
  - Build probabilistic model(s) of the compound's attributes and product profile in the context of a competitive landscape
  - Simulate development scenarios of interest

Understanding and embracing uncertainty is key to quantitative decision making and effective risk management

To simulate development scenarios of interest a number of sub-models are developed and integrated

- Sub-models differ in focus, mechanistic-depth, required disciplinary expertise, the quantity and quality of data they are developed from, and, the extent to which they serve to summarize proprietary client data



Information Sources

- **Preclinical data**
- **Early-phase trial results**
- **Late phase results**
- **In-house experts**
- **Public information**

Market economics

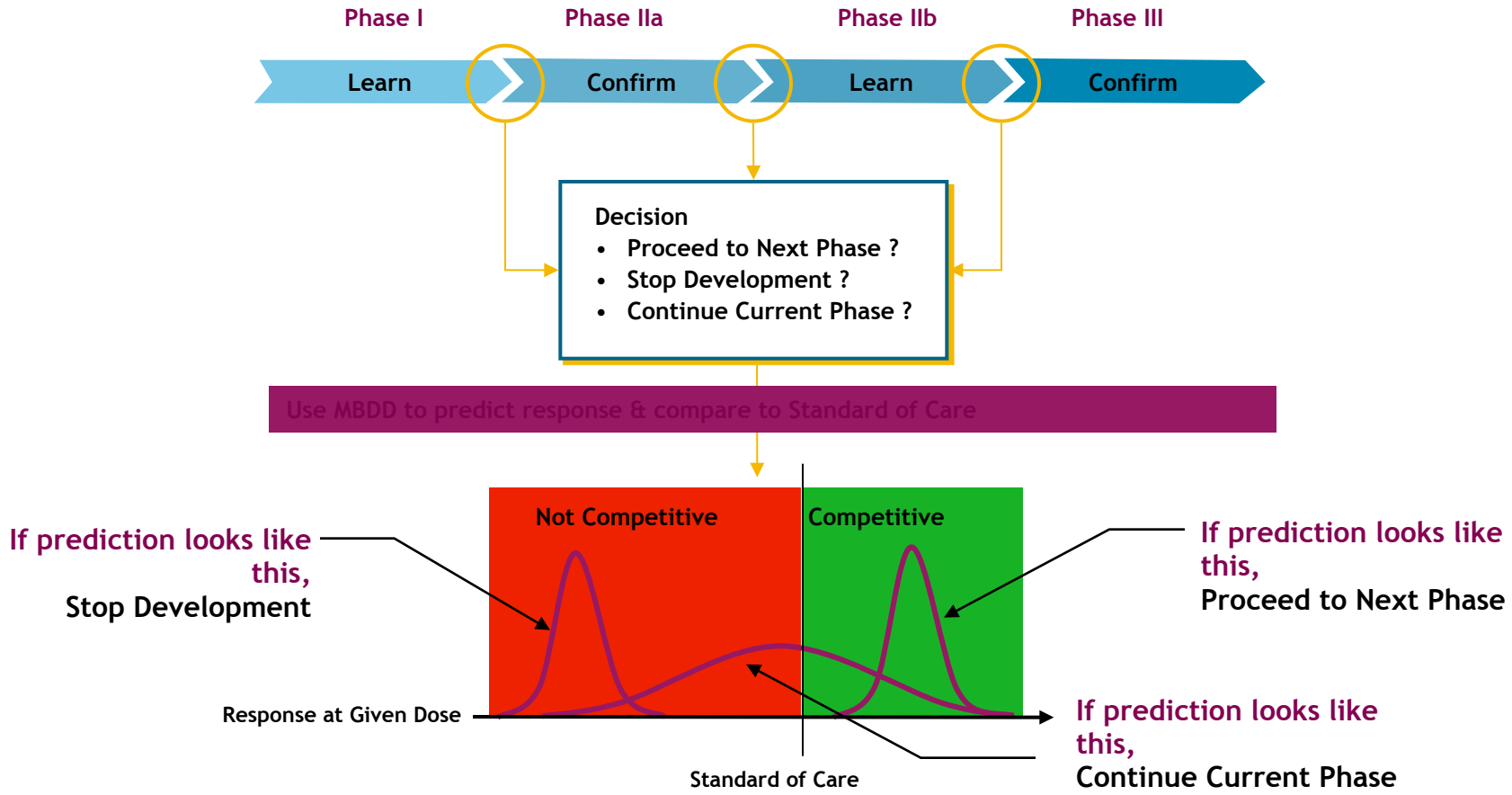
MBDD is a systematic and accountable process

- Modeling Steps
  - **Define** your next drug development decisions in terms of program value.
  - **Explore** all the proprietary data you have that is relevant to your decisions.
  - **Augment** your proprietary data with all relevant public data.
  - **Build** a mathematical, quantitative model of the complete state of knowledge relevant to your decision based upon the full data set.
  - **Qualify** our model against your data and provide you with an unambiguous description of each assumption we made in building your model.
- Simulation Steps
  - **Simulate** outcomes resulting from various possible decision scenarios using the final model.
  - **Predict** the outcome of any relevant decision scenarios and quantify the most likely result.

Leverage the above in such a way that all decisions are based on quantitative inputs

MBDD uses the Learn-Confirm[3] approach

Learn-Confirm is the context in which MBDD predicts whether program value will be maximized by proceeding to the next phase, cancelling the program or gathering more data in the current phase and then re-analyzing.



[3]Sheiner LB, "Learning VS Confirming in Clinical Drug Development," Clin. Pharmacol. Ther. 1997, 61:275-291.

Decision analysis (DA) provides a framework for extending pharmacometric models

- DA is a decision-making approach that **maximizes expected utility.**
  - Utility is a function expressing the decision-maker's preferences.
  - Utility can often be put in dollar terms—as in the examples here.
  - Sometimes it's easier to put utility on a 0-1 scale, as in Clinical Utility Index analysis trading off drug efficacy and side effects.

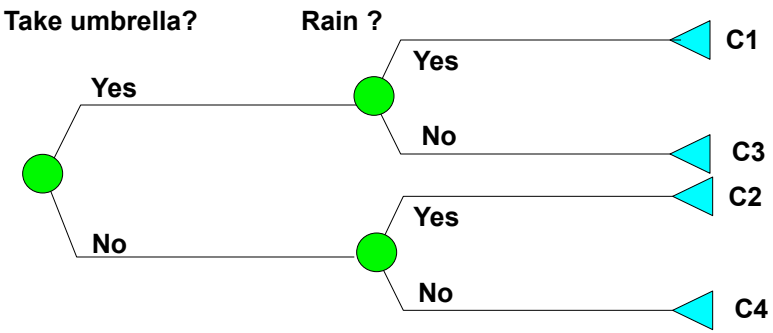
- DA is the analytical part of a six-step "Decision Quality" process to achieve a high-quality decision:
  1. Frame the problem
  2. Identify the decision-maker's values and preferences (utility function)
  3. Identify the alternatives worth analyzing
  4. Quantify the relevant information and uncertainties
  5. Calculate which alternative maximizes expected utility
     - Iterate as needed, e.g., gather more information before deciding, or try hybrid alternatives
  6. Gain commitment to action

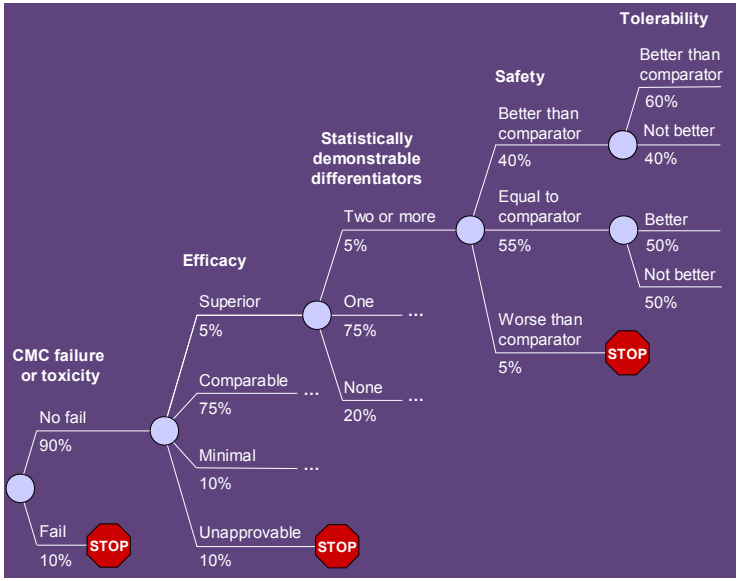
Understanding and embracing uncertainty is key to quantitative decision making

- Uncertainty itself has various meanings and levels:
  - it can refer to lack of knowledge
  - lack of certainty
  - disagreement among experts
- Sources of uncertainty :
  - Epistemic sources; those that can be reduced by further study of the system, improving our state of knowledge, etc.
  - Stochastic sources: those that are considered "unknowable"—items such as variability in the system, the chaotic nature of the system, and the indeterminacy of human systems
- Communicating uncertainty in a form that makes it useful for decision-making could be difficult :
  - Be explicit and transparent about the assumptions used to represent uncertainties, as probabilities

Decision analysis

- Decision making :
  - What alternative decisions (Ð) you are deciding among ?
  - What uncertainties Ω you face ?
  - How you value the consequences C, which consist of pairs (d,θ) where d ϵ Ð and θ ϵ Ω against each other using probability theory
  - How likely you regard each of the possible uncertain outcomes
- To make the best decisions, given your goals, maximize your expected utility with respect to your probabilities on whatever uncertainties you face.
- Bayesian analysis allows the graceful incorporation of new data as it becomes available.





Model-based DA emphasize trade-offs and uncertainty

- Direct assessment of the option's risk of false positives, negatives
- Options are compared as apples-to-apples by putting their consequences in a financial value by calculating their net present value (NPV)
- Quantify uncertainty
  - Critical for understanding the risks associated with competing decision paths
  - Necessary for assessing amount and value of learning
  - Continuously update the model with new information
  - Reduce uncertainty earlier

Integration of all available scientific knowledge and historical data is important. ***Data Is The New Gold !!***

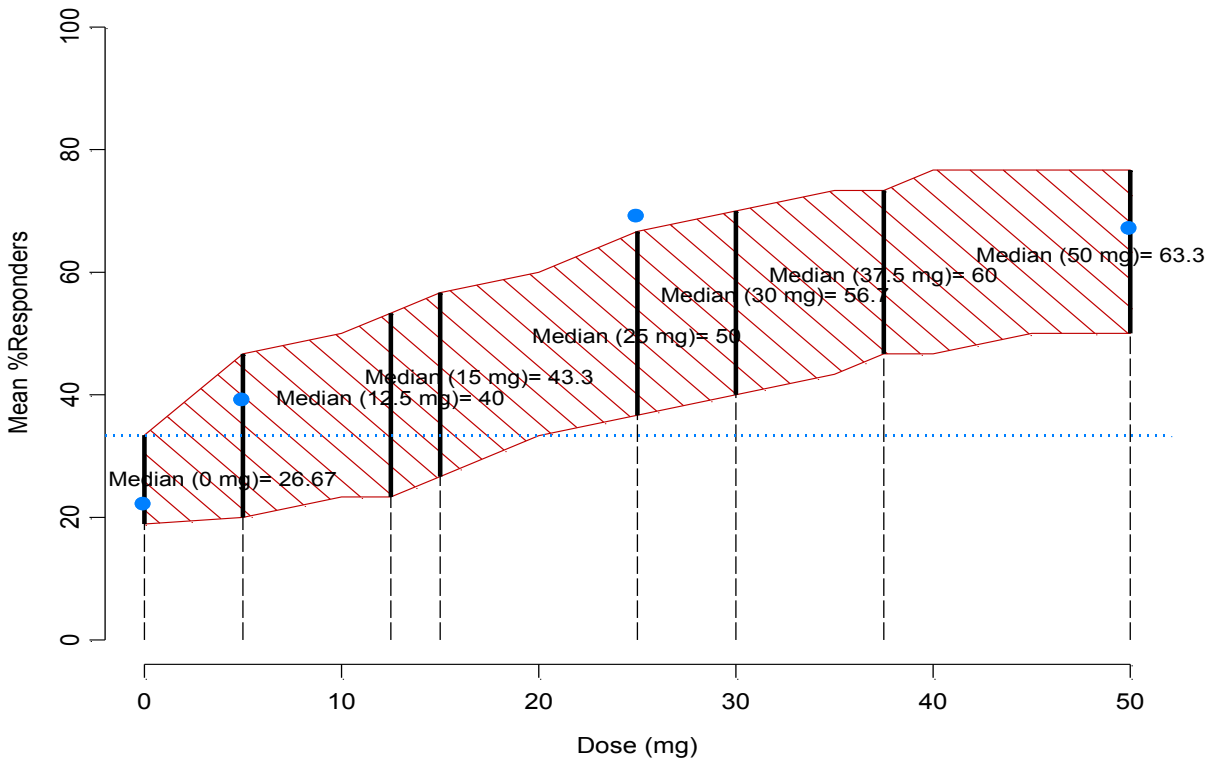
Case Study : M&S coupled with Decision Analysis

- Naloxegol is an oral selective peripheral opioid receptor antagonist. Its action restricted to organs outside the central nervous system, naloxegol blocks opiate receptors in the gastrointestinal system and reduces the incidence of Opioid-Induced Constipation (OIC) without reversal or reduction of opioid-mediated analgesia.

- Objective:
  - Evaluate the dose-response relationship to support dose selections for phase III
  - To investigate a Phase III trial design that will identify a minimum effective dose with the greatest certainty.
  - To examine the likelihood that this trial design will identify at least one dose with demonstrated efficacy.

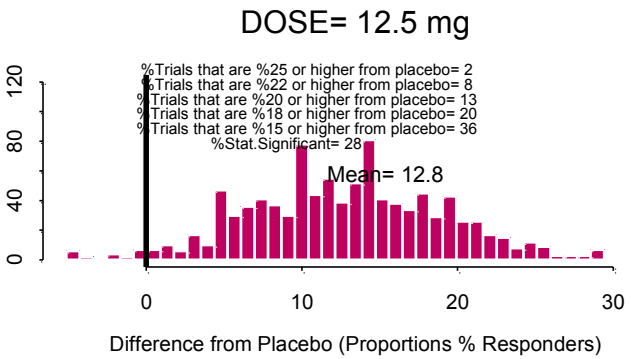
- Analysis
  - Repeated Time to event /responders
  - Develop an integrated model of response, safety and dropout rates

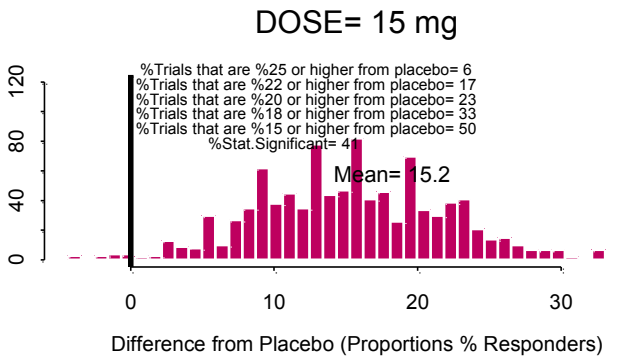
Dose Response model incorporating dropout rates for naloxegol

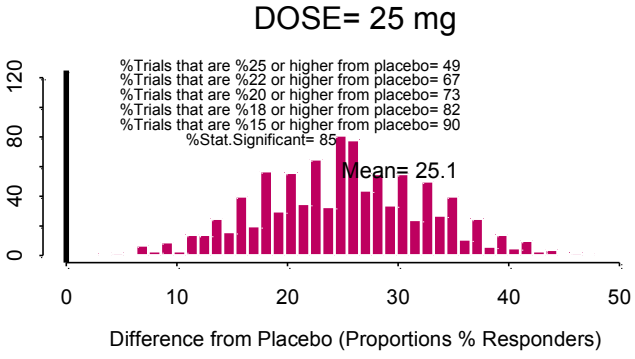


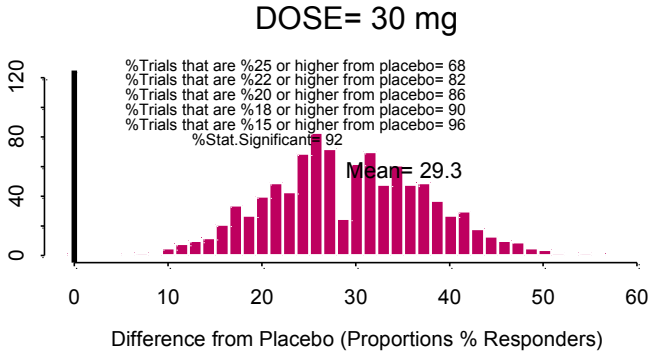
	Placebo	5 mg	12.5 mg	15 mg	25 mg	30 mg	37.5 mg	50 mg
Model Predicted %Dropout rate Median (5^{th} -95^{th})	11.1 (6.7-16.7)	13.3 (3.3-23.3)	13.3 (3.3-23.3)	13.3 (3.3-26.7)	16.7 (6.7-30.0)	20.0 (10.0-33.3)	23.3 (13.3-36.7)	33.3 (20.0-46.7)
Observed % Dropout rate	11.6	13.3	NA	NA	3.4	NA	NA	30

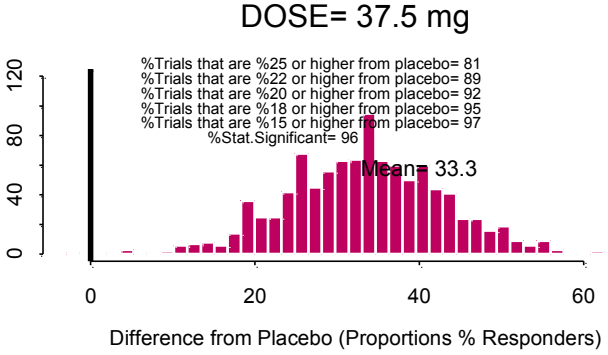
Distribution of mean (proportions) difference from placebo based on 136 patient per cohort

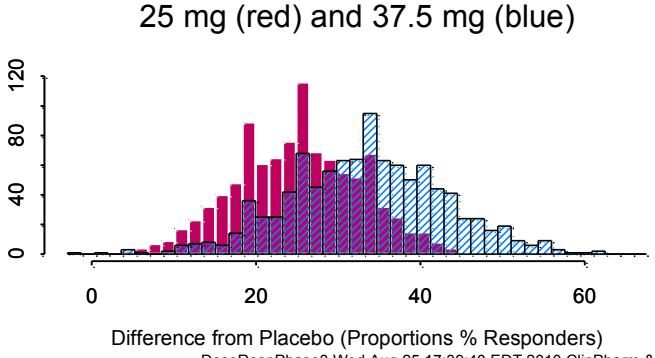








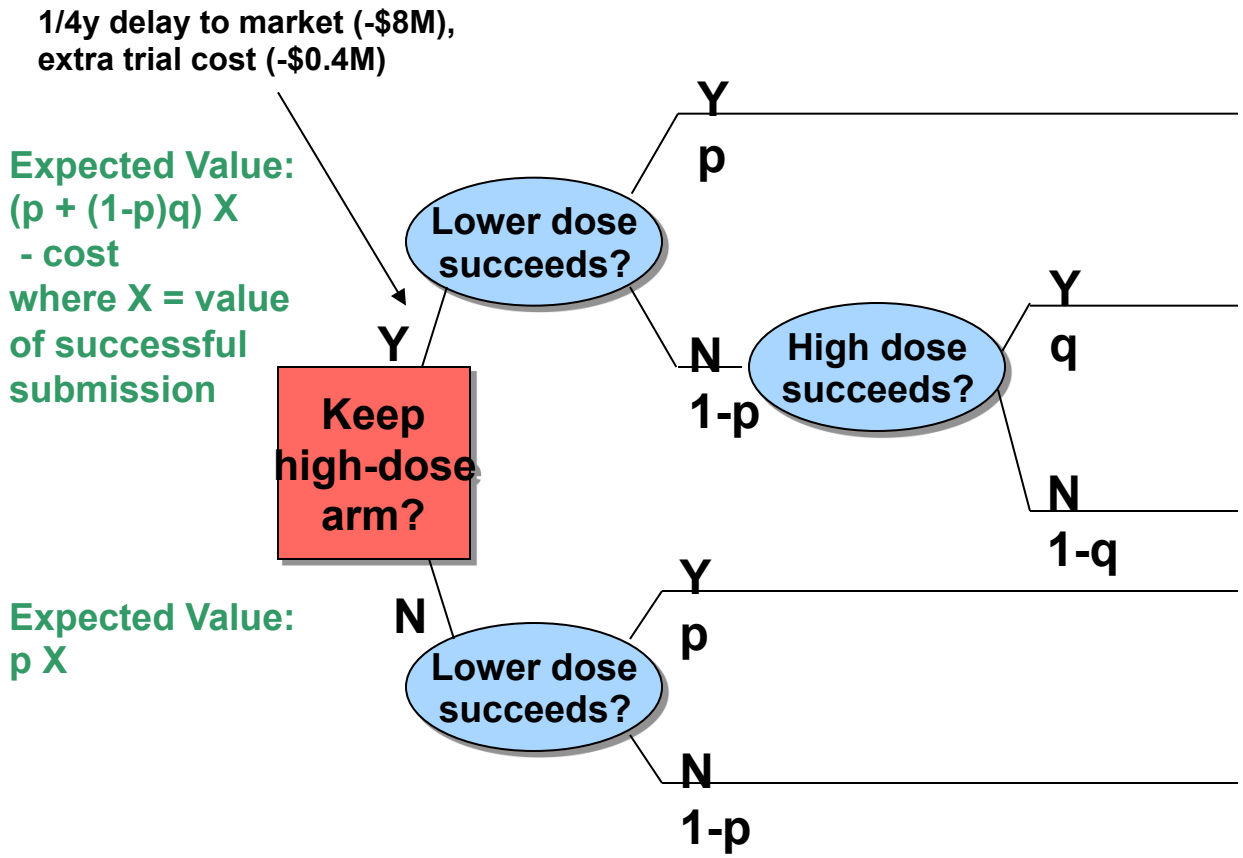




DoseRespPhase3 Wed Aug 25 17:39:40 EDT 2010 ClinPharm & DMPK

Sensitivity analysis quickly resolved a dilemma facing an HIV project team planning a 300-patient dose-finding study.

A new PK interaction study showed an unexpected reduction of the background-treatment drug at the high dose of the new drug. The team initially worried about the extra trial cost of compensating for this, and then about the delay.



Outcome

Submit with lower dose: $300M expected Net Present Value

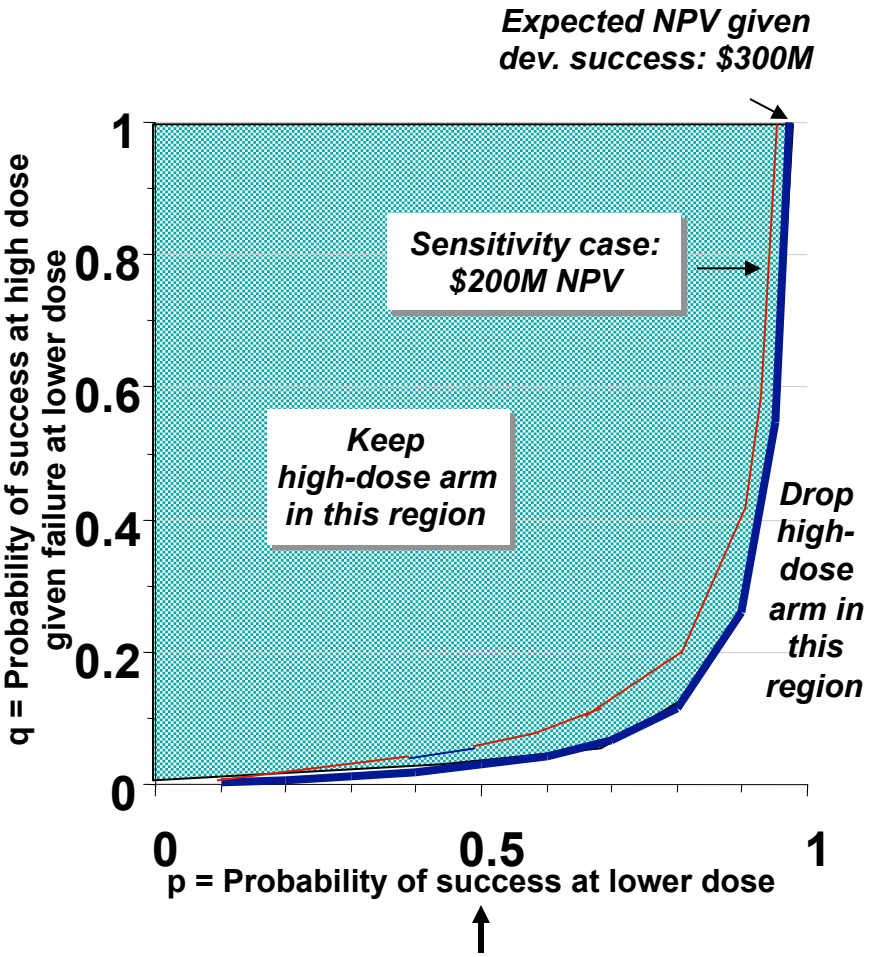
Submit with high dose: $300M

Stop (worst case): $0M

Submit with lower dose: $300M

Pick the alternative with the higher expected value...

The analysis demonstrated that only implausible combinations of success probabilities should lead to dropping the arm.



- Confirmed the decision to keep the arm, since previous modeling put $p \approx 0.5$.
- Provided confidence in the decision and alignment of the project team.
- Might have saved millions in expected value if the team would have chosen the lower-value alternative.

Last Words…

- Every Development decision is a decision about value. “how best to spend development budget and time to get regulatory approval for the most valuable label possible?”
- CUI is useful approach to support early drug development decisions
- Modeling & Simulations coupled with Decision Analysis have the potential to improve decision making
- Integrating public and proprietary data will enhance decision making