A Comprehensive Bayesian Decision-Making Framework for Drug Development

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Decision Making in Drug Development

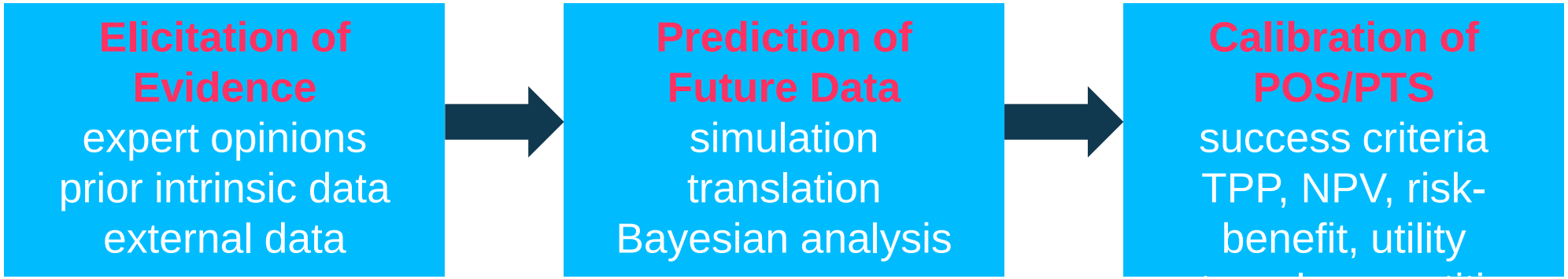
A statistician's conventional role and expanded impact

- Many decisions are made with little or without input of statisticians
- In addition to the conventional role, a statistician's contribution to decision making is more typically seen in clinical drug development, particularly working with Clinical
- There is yet more can be provided by statisticians to help make more evidence-driven decisions
- Can expand impact through collaborations with other functions (MIDD, Decision Science, Clinical Strategy, Clinical Trial Feasibility and Analytics, …)

Bayesian Quantitative Decision Making (QDM)

Bayesian predictive approach to enabling critical clinical development decisions

// Bayesian QDM Process:



// Important to account for all levels/sources of uncertainty in the process

Elicitation of Evidence

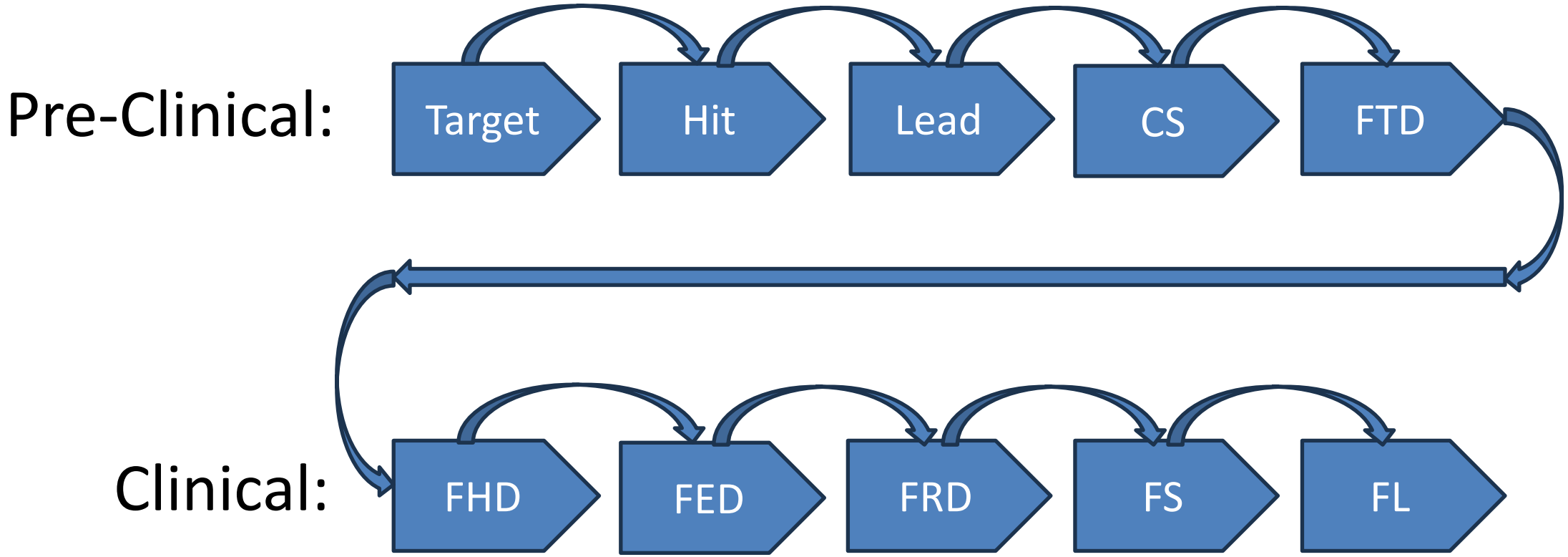
R&D Long Range Plan (LRP)

- A company's R&D strategy group predicted drug development outcomes, including R&D OPEX, WIP, revenues, etc., for the next 10 years or so for the R&D Sr. Management to make adjustments and achieve near-term and long-term goals in alignment with company vision
- There were key sources of information important for making LRP prediction, but were as yet not been utilized properly

R&D Productivity

$$P \alpha \frac{WIP \cdot p(ts) \cdot V}{CT \cdot C}$$

Drug Development Roadmap



Long Range Simulation Modeler

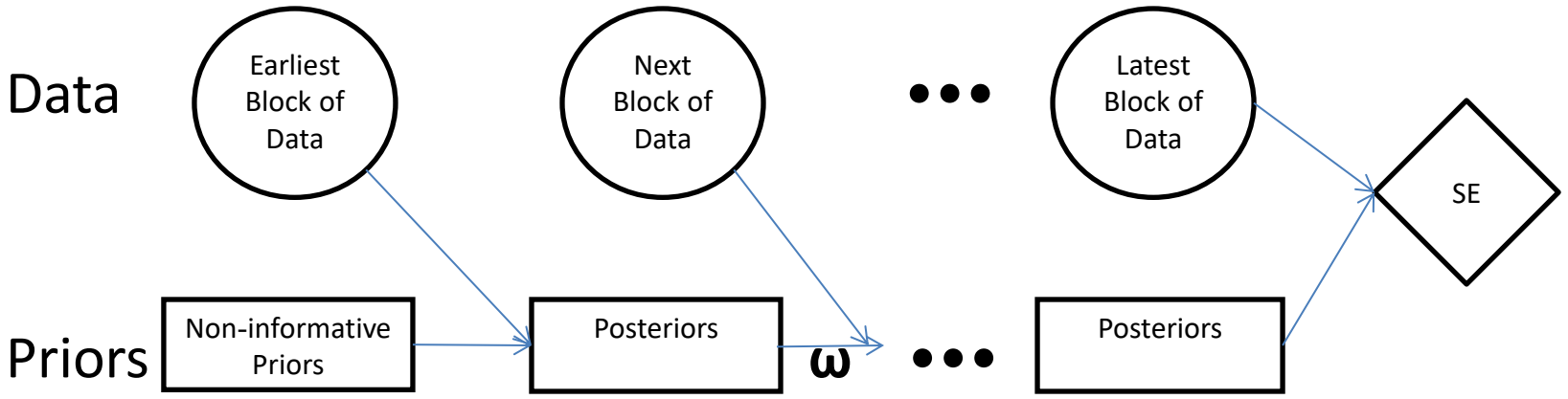
- The company used a Simulation Environment (SE) for research LRP prediction
- The SE took “many” inputs, such as FTEs, pipeline, NILEX, …, and simulated outputs, including OPEX, revenues, …

Problem with Conventional Practice

- Data such as cycle time (CT), cost (C), etc. were summarized and used as single estimates without consideration of variability
- Triangular distributions were proposed as substitutes later on
- Question: Is there an even better way to elicit LRP source data for more accurate and precise prediction?

Iterative Information Elicitation

- Data such as cycle time, cost, etc. changed through years
- Recent data would be more relevant, while more distant data were not all non-informative
- Applied different weights to periods of years, for example, with a continual deflation weight (**ω≤1**) by the following iterative procedure



Development Phases

Source information were broken down to the development phase level:

Target-HIT, HIT-Lead, Lead-CS, CS-FTD, FTD-FHD

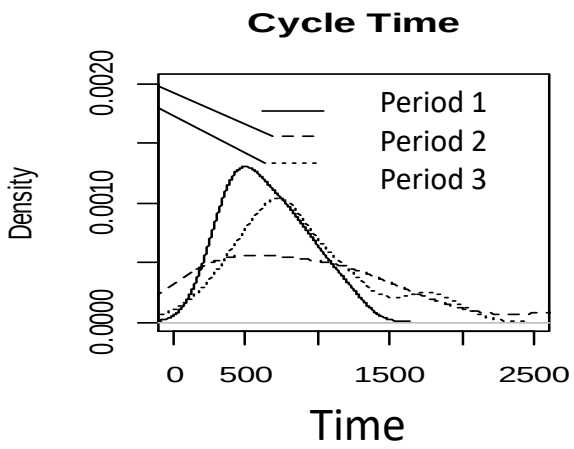
FHD-FED, FED-FRD, FRD-FS, FS-FL

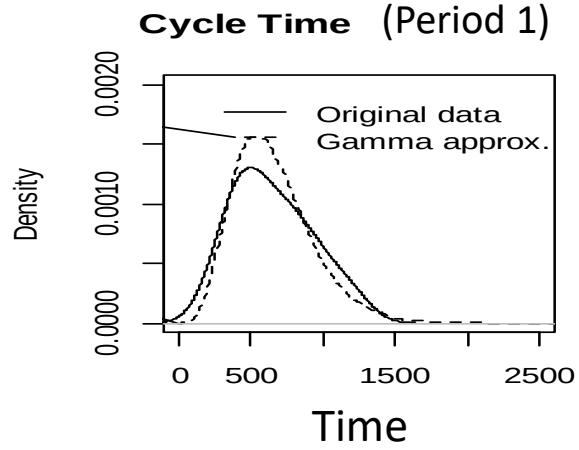
Bayesian Generalized Linear Models

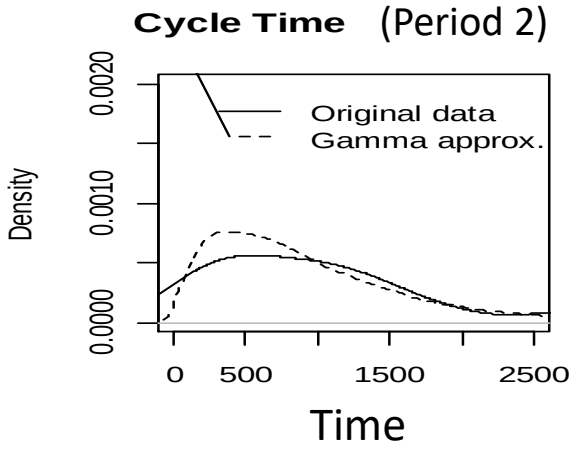
- Normal or log-linear models did not fit the LRP source data well
- GLMs such as gamma generalized linear models appeared to work better

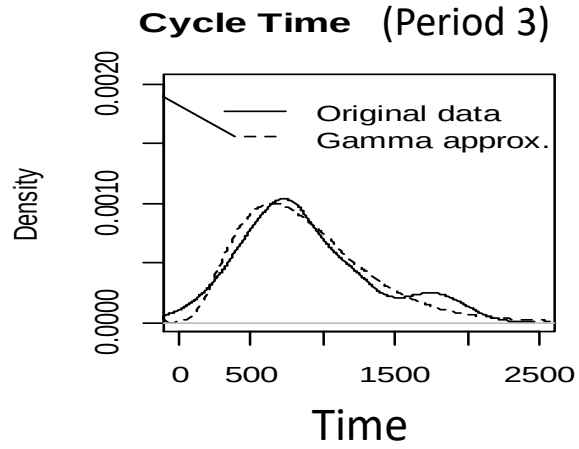
Bayesian Modeling of Cycle Time

- For a development phase:



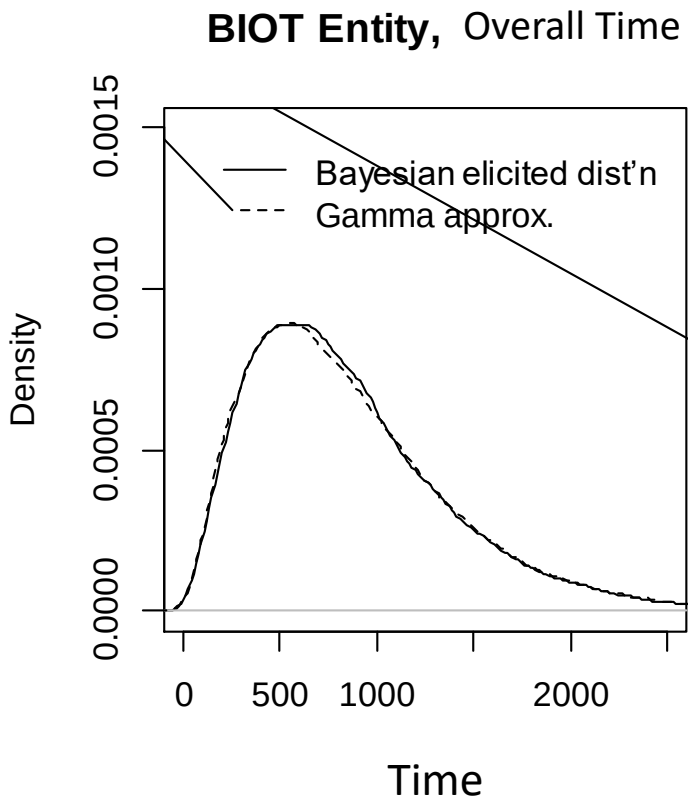


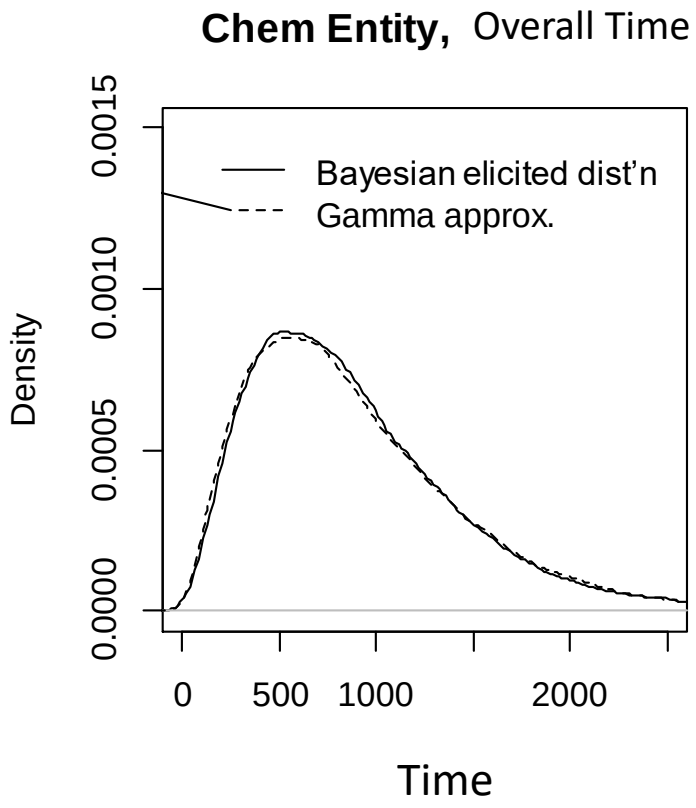




Bayesian Modeling of Cycle Time (Cont'd)

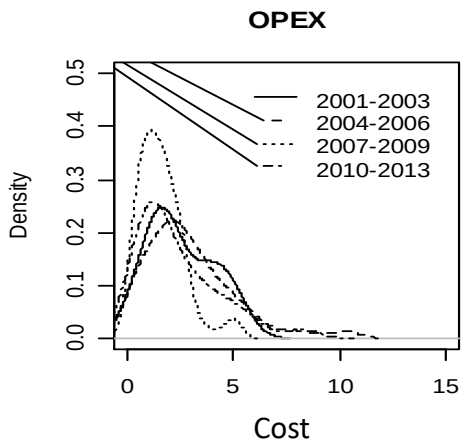
- Good overall gamma approximation:

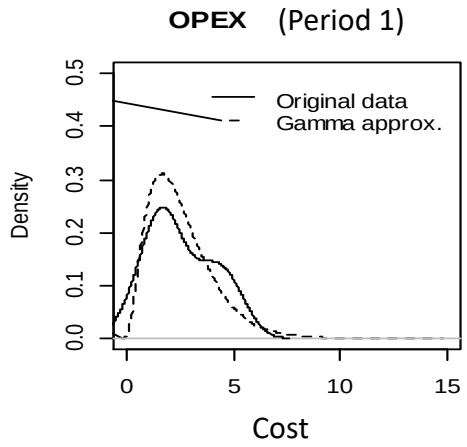


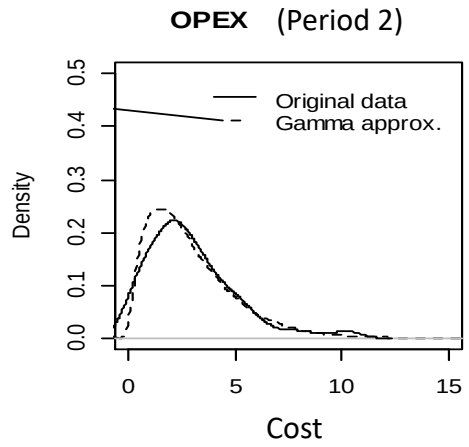


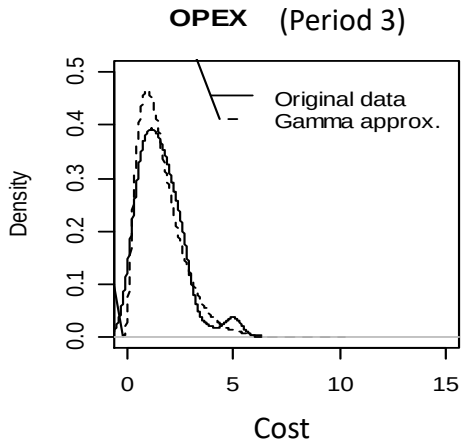
Bayesian Modeling of OPEX

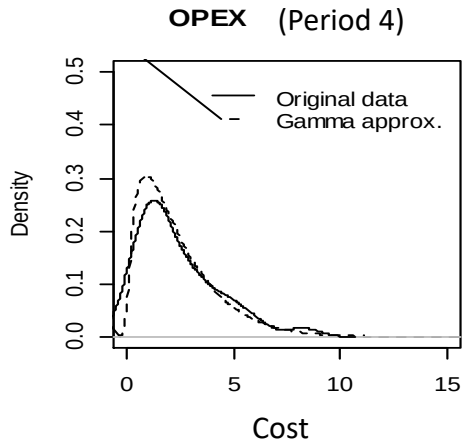
- For a development phase:





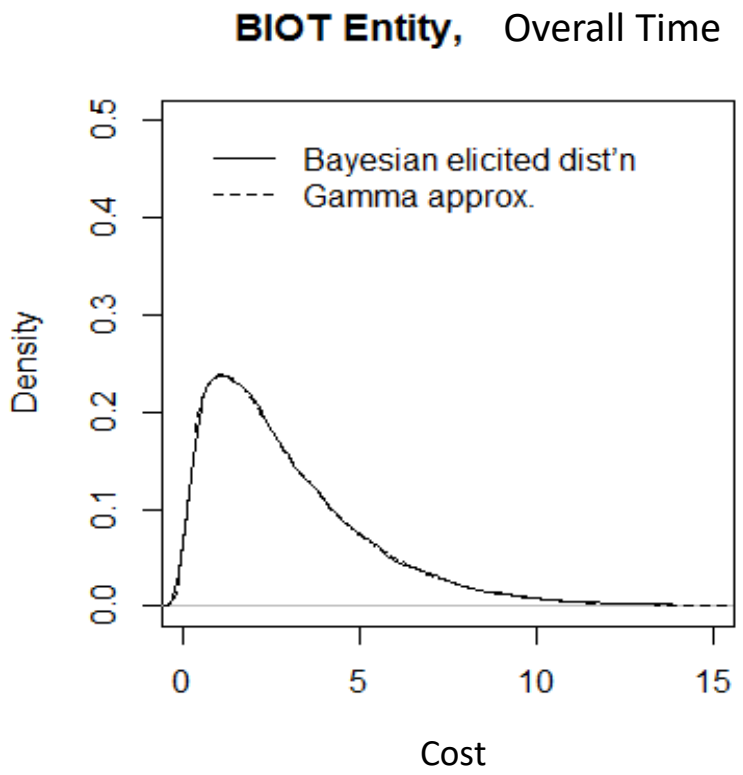


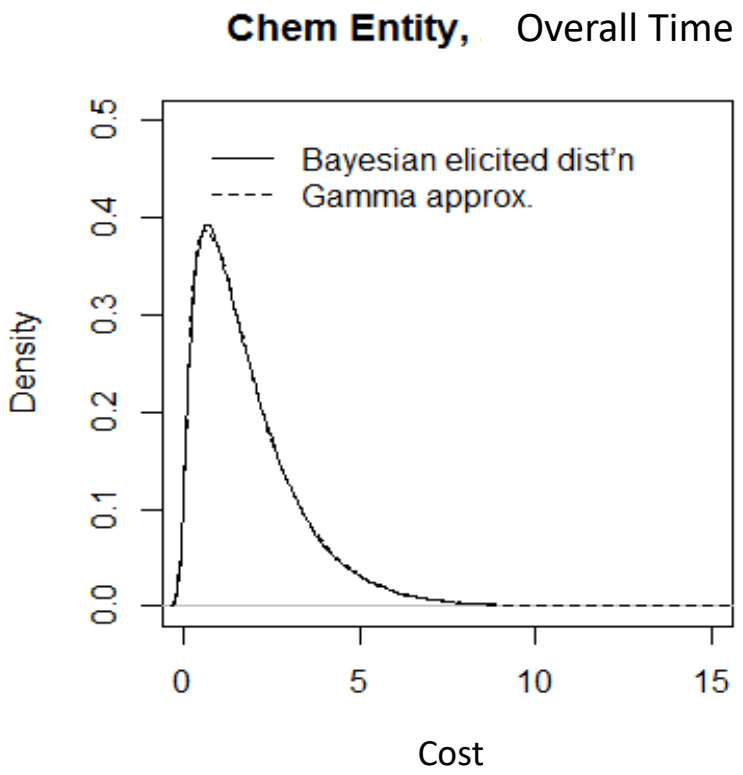




Bayesian Modeling of OPEX (Cont'd)

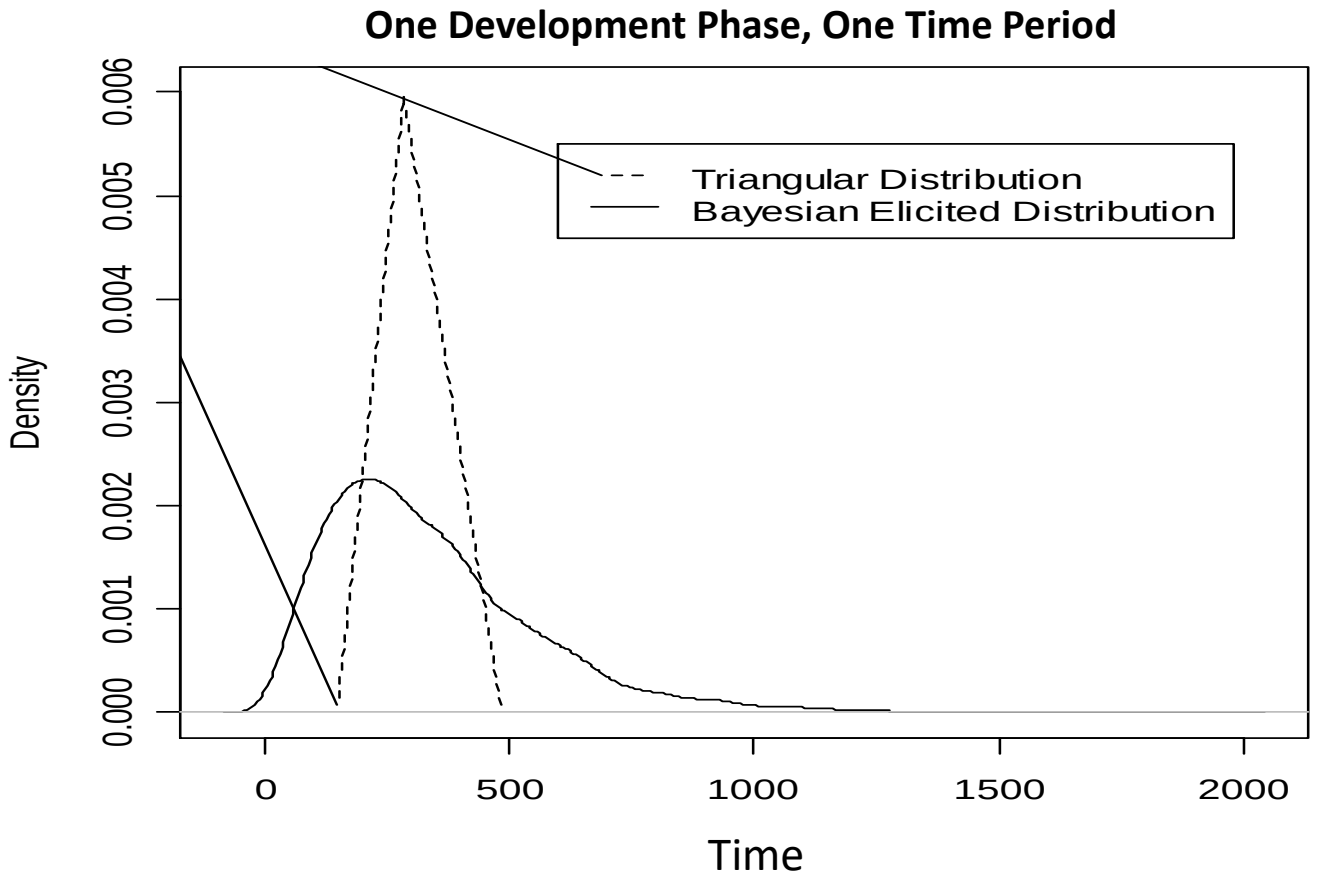
- Good overall gamma approximation:





Much Improved Elicitation

- Triangular distribution too crude an approximation



Key Points

- Statisticians can help improve evidence elicitation in practices and decision making beyond the conventional role
- Expand collaborations with other functions

Prediction of Future Data

A Real Case

Use Ph1 data to predict Ph3 POS

- A clinical program currently in Ph2 development, with an ongoing Ph2 trial
- A small Ph1 trial was previously completed
- Team needs to understand Ph3 POS with varying design factors (sample size, treatment follow-up duration, …)
- Primary endpoints for Ph1 and Ph2 trials are same biomarkers
- Planned Ph3 trial has a time-to-event primary endpoint
- Use observed Ph1 biomarker effects to predict Ph3 POS (event-driven)
- Critical considerations in prediction:
  - Variability of elicited translation of biomarker effects to clinical effect (i.e. event hazard reduction)
  - Variability of yet blinded Ph2 data

Prediction with Adequate Consideration of Uncertainty

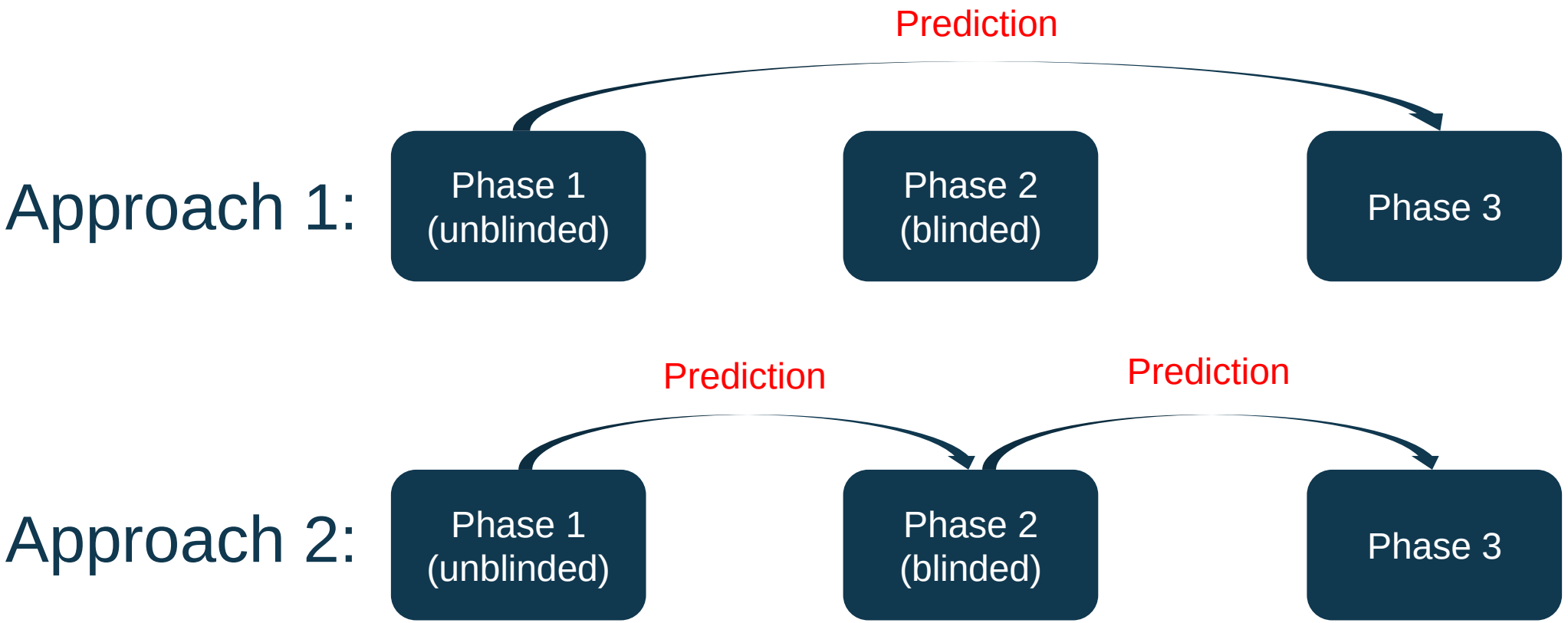
Decision for initiating early Ph3 preparations

A hypothetical scenario:

- A drug candidate in Ph2 development:
  - A completed Ph1 trial (2-arm, 50 subjects/arm, unblinded)
  - An ongoing Ph2 trial (2-arm, 100 subjects/arm, blinded)
  - In the planning stage for a Ph3 trial
  - Same binary primary endpoint for all phases
- Question: should team initiate early Ph3 preparations while the Ph2 trial is ongoing?

Prediction Approaches

Which is correct?



Assumptions

A drug development scenario

- Completed Ph1 results:
  - Treatment response: 40/50
  - Control response: 30/50
- Ongoing Ph2 design (blinded):
  - 100 subjects per arm
- Planned Ph3 design:
  - 200 subjects per arm
  - Primary comparison: response rate difference
  - Analysis: t-test

Approach 1

Use Ph1 data to predict Ph3 POS w/o consideration of Ph2

- Summary of Ph1 data as prior distributions:
  - Treatment response rate: $Beta(40 + 0.5, 10 + 0.5)$
  - Control response rate: $Beta(30 + 0.5, 20 + 0.5)$
- Use the prior distributions to simulate the Ph3 trial repeatedly:
  - Calculate the p-value for each simulated trial
  - $POS = \Pr(p - value < 0.05) = 0.87$

Approach 2

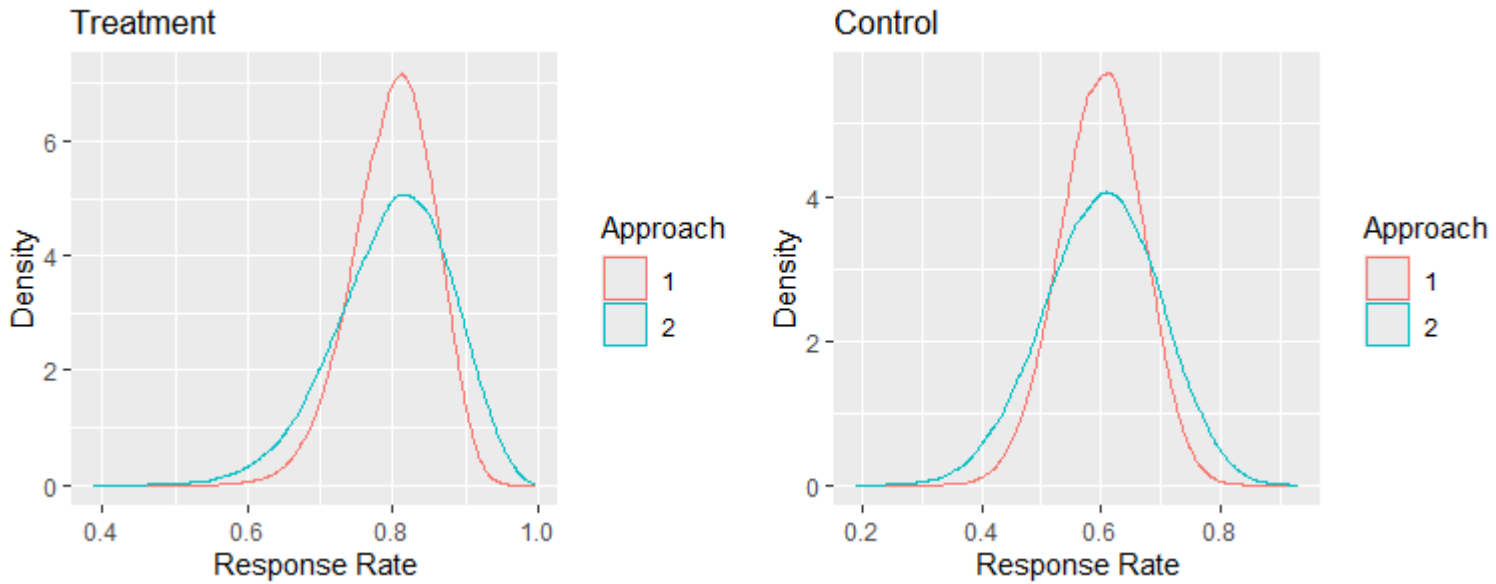
Use Ph1 data to predict Ph3 POS with consideration of Ph2 data

- Summary of Ph1 data as prior distributions as in Approach 1
- Use the prior distributions to simulate the Ph2 trial repeatedly:
  - Conduct Bayesian analysis of each simulated trial and obtain posterior distributions for the treatment and control response rates
  - Use the posterior distributions as priors to simulate the Ph3 trial
    - Calculate the p-value for each simulated trial
    - $POS = \Pr(p - value < 0.05) = 0.82$

Comparison of Approaches

Different priors used in the approaches

// Priors used in Approach 2 are more diffused due to added Ph2 uncertainty

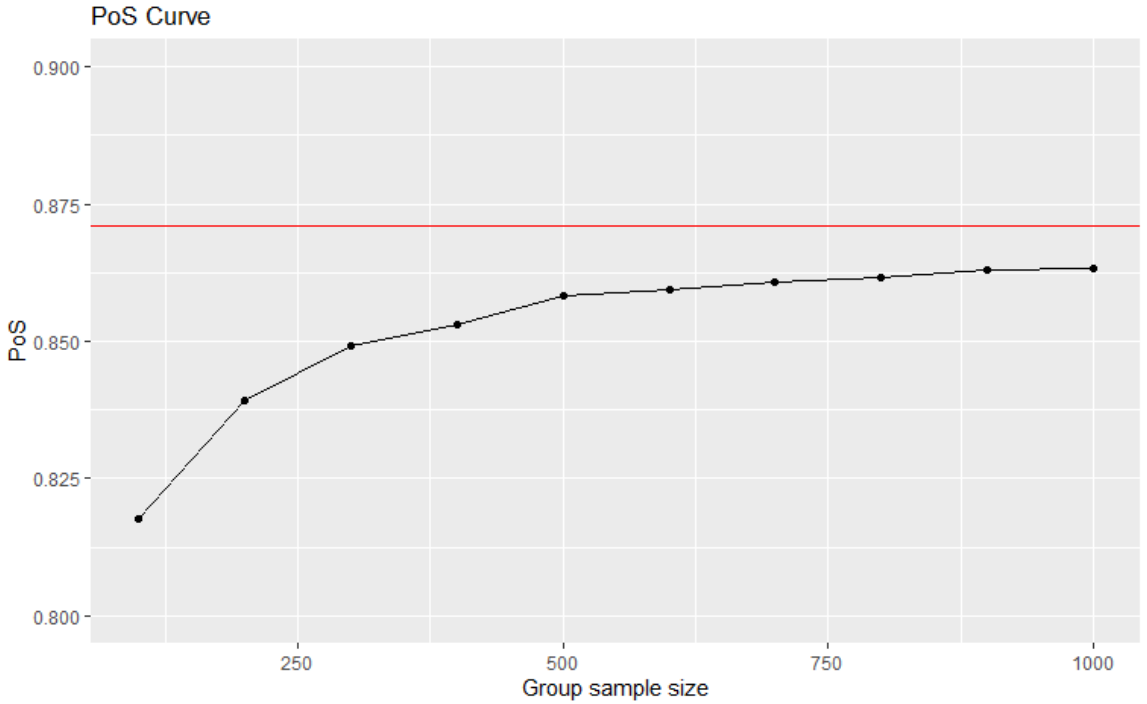


// More diffused priors result in a lower predicted Ph3 POS

Convergence of Priors with Increased Ph2 Sample Size

Impact of Ph2 sample size in Ph3 prediction

// Impact of Ph2 sample size on Ph3 POS:



// Update Ph3 POS once Ph2 data are unblinded

Key Points

- Ignorance of uncertainty would result in over-optimistic prediction
- The best knowledge for prediction is whatever currently at hand, which cannot by simulation/prediction be enhanced to increase probability of success

Calibration of Success

QDM for A Clinical Program

QDM in practice

- QDM tasks:
  - Monitoring of Ph1 dose escalation
  - Go/no-go for dose expansion
  - End of Ph1 decisions
  - Asset selection
  - Ph2/3 pivotal study design
  - Comparative effectiveness analysis
  - Development of Shiny apps
- What outputs are clear and informative to the team for decision making?

QDM Output Examples

Communication of QDM analysis

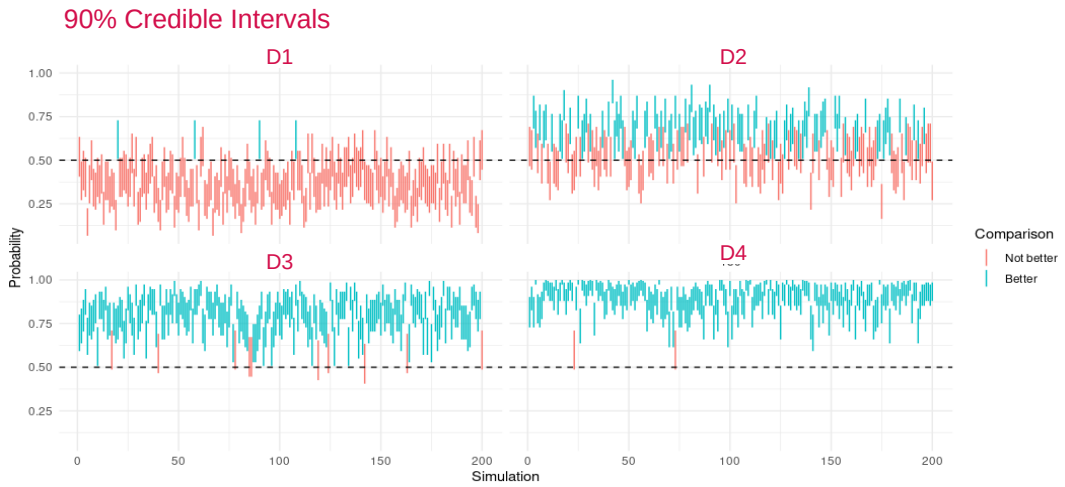
Esset efficacy (E) performance:

Dose	$\Pr(E \leq c1)$	$\Pr(c1 < E \leq c2)$	$\Pr(E > c2)$
1	0.590	0.365	0.045
2	0.066	0.419	0.515
3	0.002	0.062	0.937
4	0.000	0.004	0.996

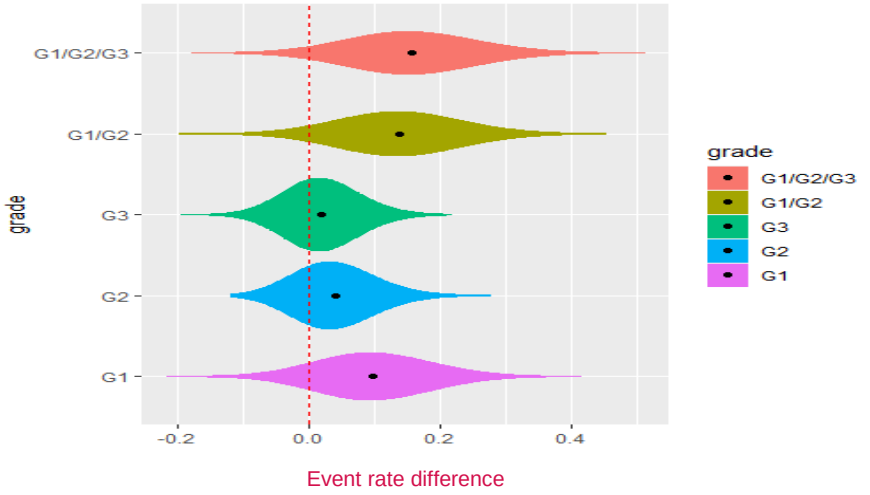
Safety relative to competitors:

AE Grade	Competitor	
	1	2
G1		0.09
G2		0.36
G3	>0.99	0.99
G1/G2	0.29	0.12
G1/G2/G3	0.60	0.78
Green: ≥0.70, red: ≤0.3, blue: between 0.3 and 0.7		

Efficacy performance of simulated trials:



Safety between assets:



Key Points

- Communication of QDM outputs clear and informative to decision makers
- Good to show variability of prediction
- Graphical and tabular presentations are both helpful

References

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Health for all, Hunger for none

Thank you!

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