Prior Elicitation as Input to a Phase 3 Study Probability of Technical Success (PTS) Calculation

Niki Arya

Statistical Science Associate Director, AstraZeneca

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Outline of Presentation

- Elicitation Definition/Background
- Details of the Expert Elicitation Process
- Incorporation of Expert Elicitation into the Prior Assumptions
- Prior assumptions to Determine the PTS of the Phase 3 Study
- Summary of Expert Elicitation Approach

Elicitation

- Elicitation is a scientific method to develop judgments.
- Elicitation aims to develop well-informed, unbiased expert judgments.
- Experts should have knowledge of the pertinent data and awareness of the biases/limitations.
- Frequently used by pharmaceutical companies to determine the PTS for different outcomes e.g. successful clinical trial. The PTS calculations support and guide investment decisions.

Elicitation Process

- Prepare and distribute an evidence dossier with relevant data e.g., results from previous similar trials.
- Define the questions of interest for elicitation.
- Identify the experts.
- Present evidence dossier to the experts and obtain responses to the elicitation questions.
- Combine the expert responses/judgments into a single prior belief.
- Use the prior info to calculate the assurance/PTS.

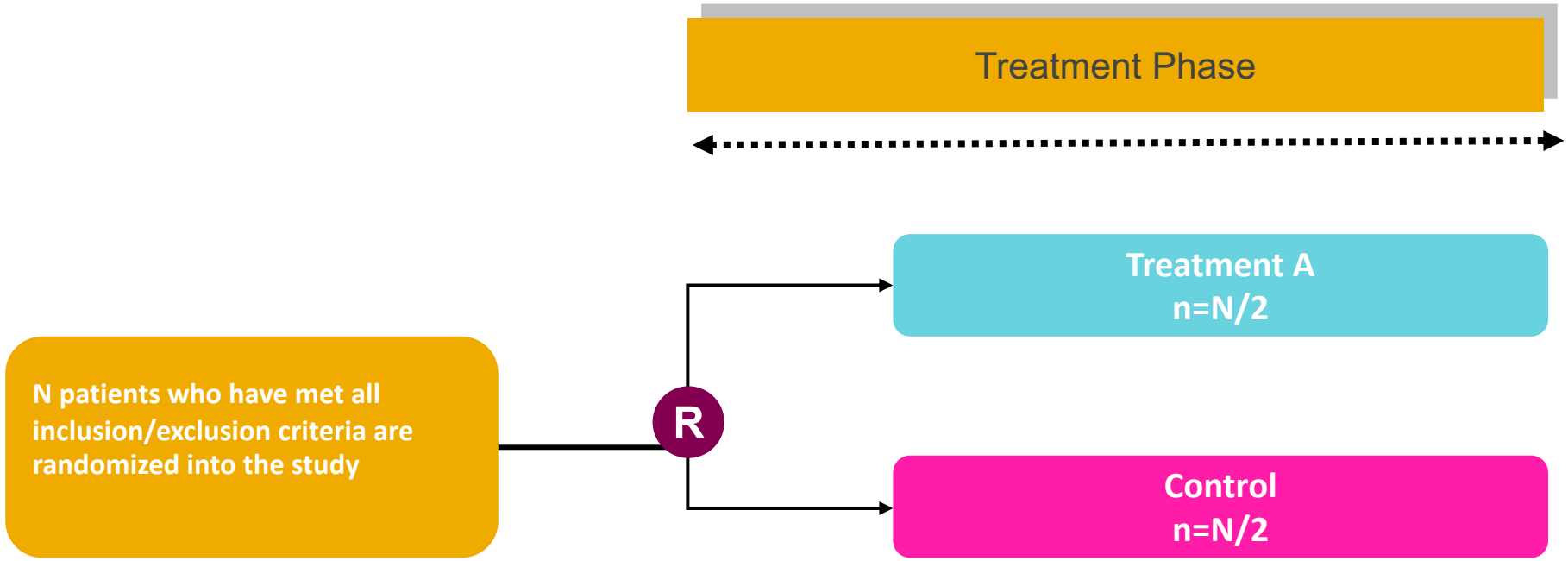
Elicitation Process (continued)

- Expert elicitation to determine the prior assumptions needed to calculate the probability of technical success (PTS) for a planned large outcome study for one of our products.
- Primary endpoint is a composite endpoint with subcomponents that are secondary endpoints.
- Evidence dossier prepared summarizing the results from previous trials with our drug and other drugs within the same class.
- In these previous trials, a similar composite endpoint and the individual subcomponents were analyzed in slightly different populations to help shape prior assumptions about the effects of our drug on the primary endpoint proposed in our large outcome study.
- This presentation was shared with a panel of 6 experts in this field who then used these results to predict the expected treatment effect on the primary composite endpoint and each of its subcomponents in the population proposed for the planned large outcome study.
- These predictions were then pooled together and weighted appropriately based on the expertise of the panelist to form a prior distribution which was then used to determine the PTS for the planned large outcome study.

Study Design

Objective

To assess the effect of our product (Treatment A) relative to the control on reducing the risk of the primary composite endpoint.



Primary endpoint: Time to first of the events in the composite endpoint

Secondary endpoints:

- Time to first Subcomponent #1 event
- Time to first Subcomponent #2 event

Elicitation Approach

- Elicitation approach implemented, asking the following questions to the panel of experts:
- Given the information presented in the evidence dossier and your prior knowledge about the products, what is the expected treatment effect (Hazard Ratio) of Treatment A relative to Control in reducing the incidence of:
  - the primary composite event?
  - the subcomponent #1 event?
  - the subcomponent #2 event?
- Panel of experts: 3 physicians and 3 statisticians

Outcomes of Prior Elicitation – Raw Data*

	Q1 – Time to Composite Endpoint (HR)			Q2 – Time to Subcomponent #1 (HR)			Q3 – Time to Subcomponent #2 (HR)		
	P10	P50	P90	P10	P50	P90	P10	P50	P90
Expert #1	0.35	0.8	0.99	0.5	0.75	0.9	0.6	0.85	0.9
Expert #2	0.65	0.8	0.99	0.6	0.8	0.95	0.65	0.8	0.95
Expert #3	0.7	0.8	0.9	0.6	0.8	0.9	0.7	0.85	0.9
Expert #4	0.6	0.8	0.95	0.3	0.75	0.9	0.6	0.75	0.9
Expert #5	0.7	0.8	0.9	0.7	0.85	0.95	0.7	0.85	0.95
Expert #6	0.6	0.7	0.8	0.55	0.65	0.75	0.75	0.85	0.95

* Values shown are not the actual numbers- these are representative data for the purpose of the presentation.

Outcomes of Prior Elicitation*

Custom Weighting	Mean fitted gamma distribution (HR)		
	Q1 – Primary Composite Endpoint	Q2 –Subcomponent #1	Q3 –Subcomponent #2
	0.704	0.608	0.809

Proposal made (prior to results being seen) to use custom weighting to give less weight to estimates provided by the less-experienced panelists

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Assurance

- The unconditional probability of a positive trial outcome
- Depends partly on what we already know (believe) about the treatment effect and partly on the trial design
- Important in estimating probability of success in a pivotal Phase 3 trial
- Enables one to quantify the probability of success by considering what effect sizes are plausible
- Calculated by weighting together the power for different likely effect sizes

Assurance for Phase 3 Trial

- Successful outcome defined as achieving certain hazard ratio estimates for the primary and secondary endpoints.
- Assurance for Phase 3 study calculated using simulations run in R.
- Sampled observed HR estimates for key endpoints in Phase 3 trial from prior gamma distributions generated from expert elicitation.
- Simulated Phase 3 trial data based on these observed HR estimates and determined whether or not each simulated trial was ‘successful’. Success determined by comparing the observed estimate to a critical value.
- Assurance = # of Successes/ # of Simulations

Summary

- Expert elicitation is used along with more straightforward assurance calculations and industry benchmarks to determine PTS.
- Selection of the ‘right’ experts is critical for a reliable PTS calculation. Determining the appropriate weight to give to each expert can be challenging.
- As there is some subjectivity involved in expert elicitation, it is important to provide a comprehensive set of results from previous similar clinical trials to guide the experts when they provide their estimates i.e., make the process as ‘objective’ as possible.
- Evaluation of the expert elicitation approach is evolving as more trials use it.