

# Futility Analysis

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# Background and Notation

- Standard therapy versus new therapy
- Time-to-event outcome
- Test of log hazard ratio  $H_0:\theta\geq 0$  versus  $H_1:\theta<0$ 
  - $H_1:\theta<0$  implies new therapy is better than standard therapy (superiority)
  - $H_0:\theta\geq 0$  implies there is no difference between two regimens or the new therapy is worse than standard therapy
- $\delta<0$  represent the clinically significant value of  $\theta$  that is used to power the study

# Four Major Approaches

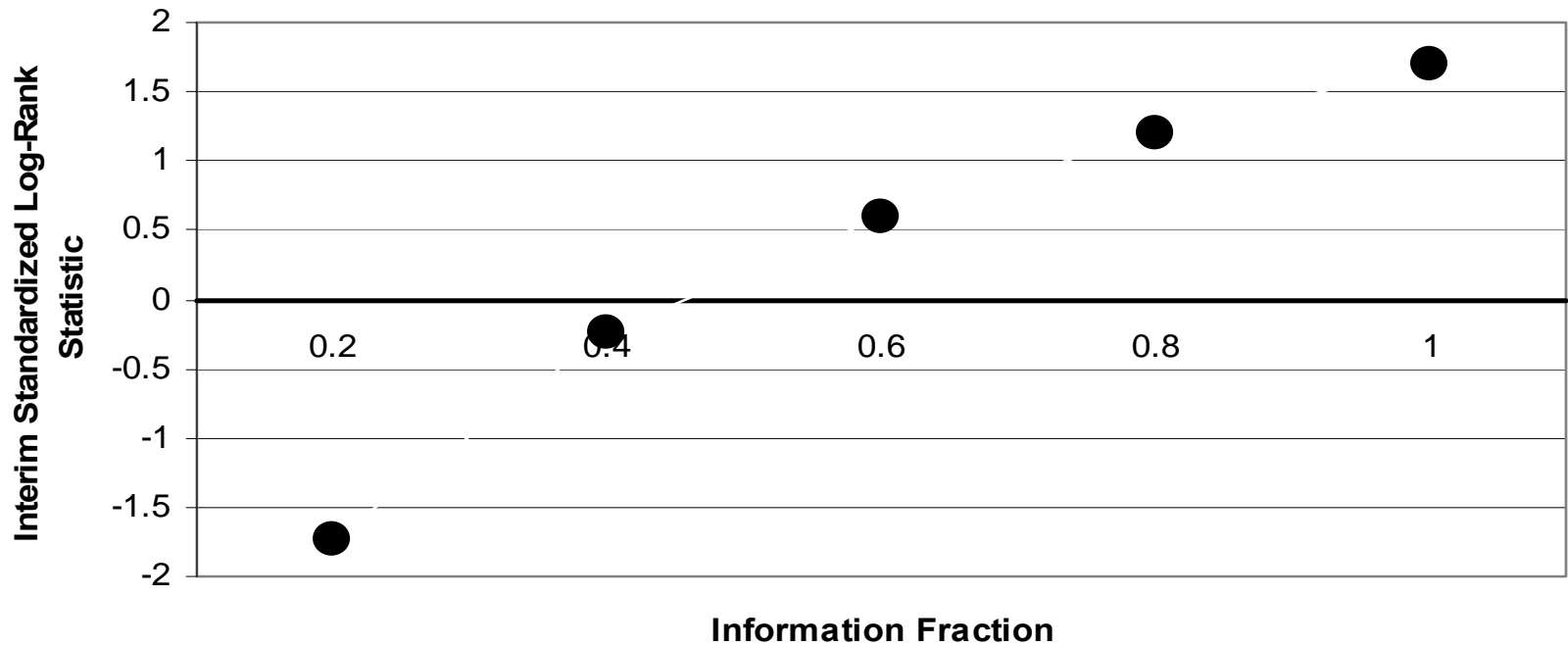
- **Group Sequential**
- **Stochastic Curtailment**
- **“Mixed” Bayesian**
- **“Pure” Bayesian**

# Preliminary Comments

- Four different mathematical formulations.
- Same conclusion at any interim analysis.
- Mathematical commonality.

# Group Sequential Approach

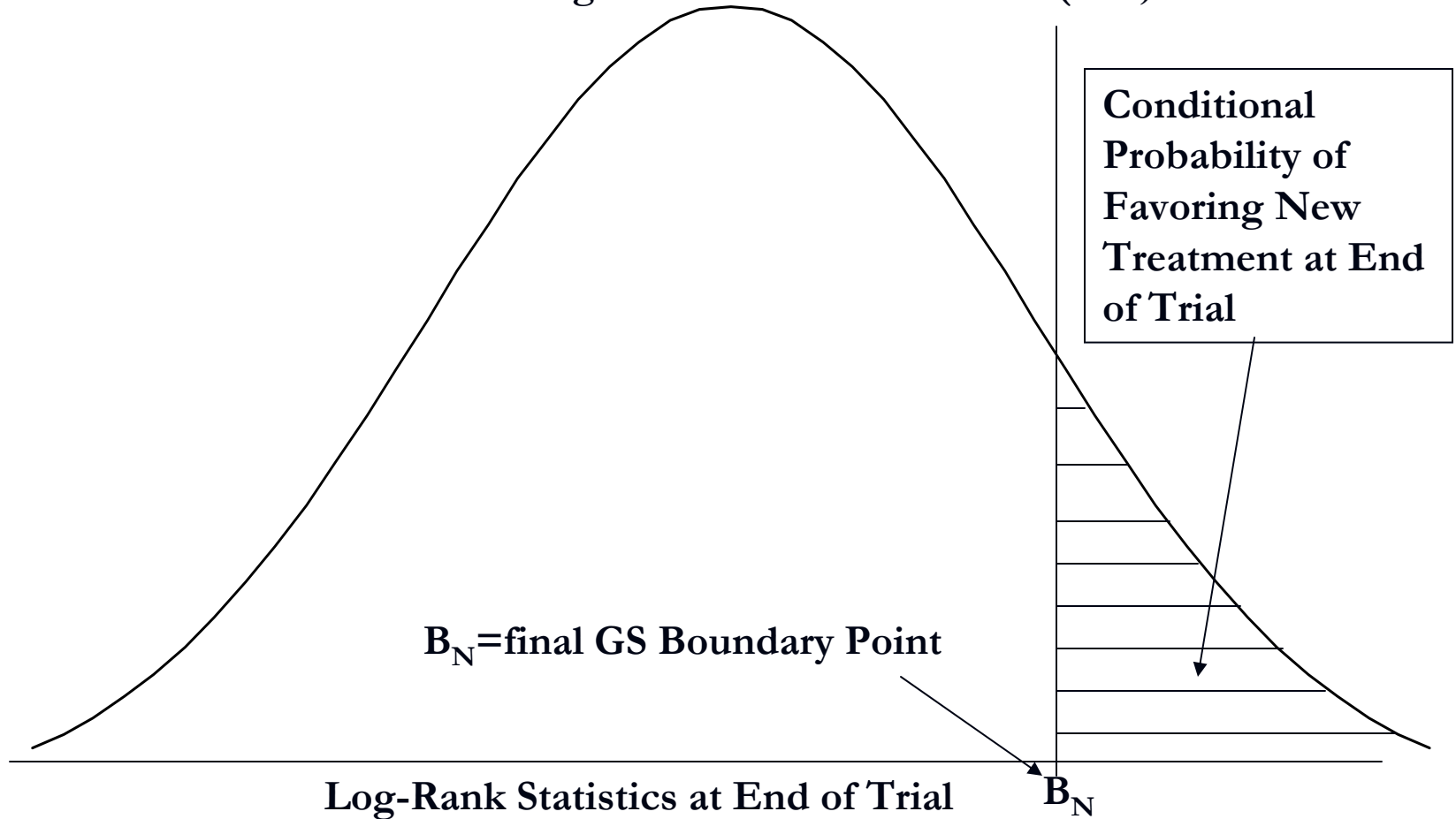
**O'Brien Fleming Futility Boundaries**  
Maintains Overall Type I Error=0.05, Type II Error=0.90



# Stochastic Curtailment

Conditional Distribution of Log-Rank Statistic at End of Trial

Given Interim Log-Rank Statistics and  $\theta < 0$  ( $\theta = \delta$ )



# Relationship Between Stochastic Curtailment and Group Sequential Approaches

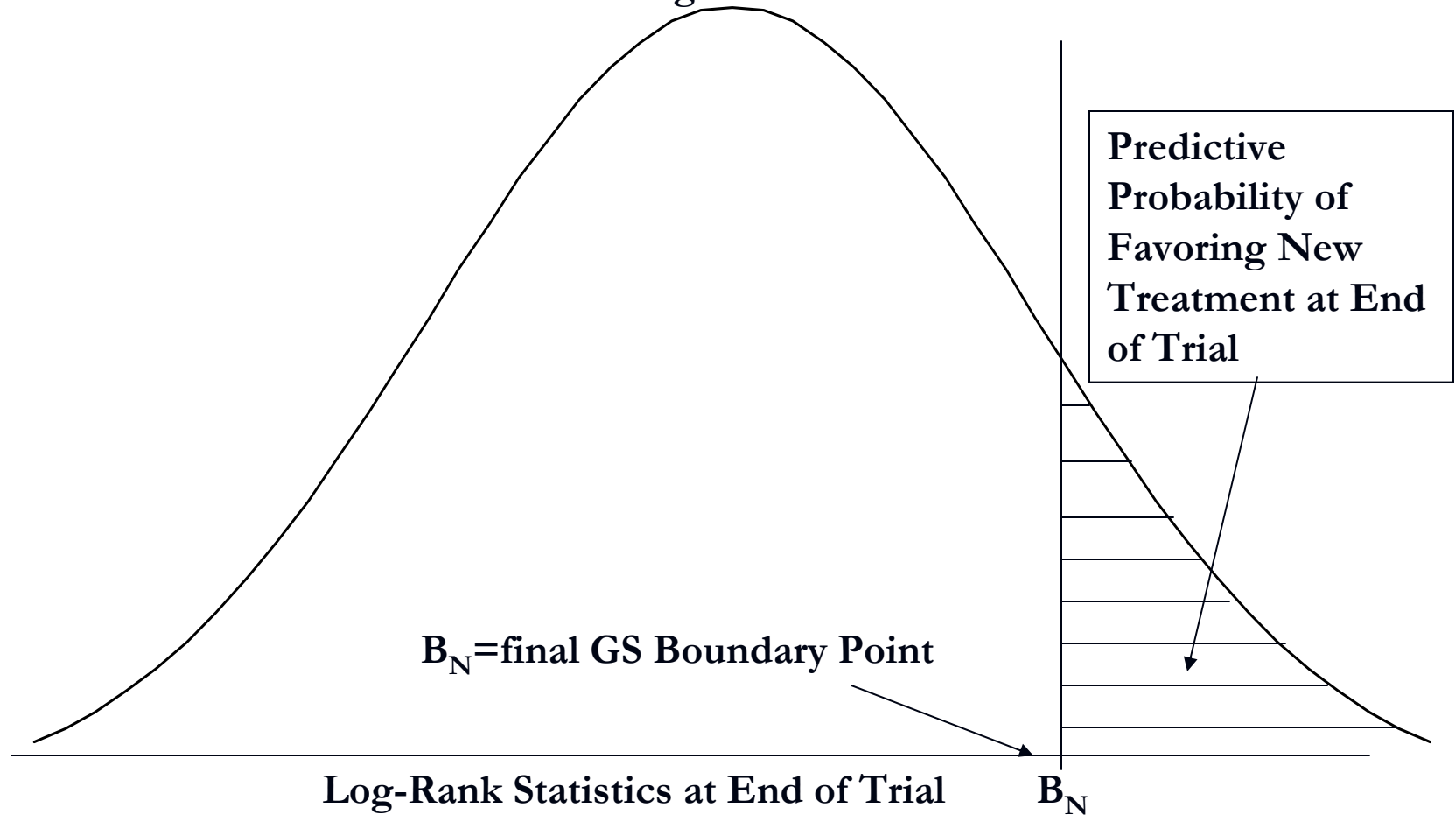
## Example

- Suppose the interim log-rank statistic equals the O'Brien/Fleming group sequential futility boundary.
- Group Sequential approach: Stop trial.
- Stochastic curtailment conditional probability equals 0.5 when  $\theta = \delta$ .

# “Mixed” Bayesian Approach

Predictive Distribution of Log-Rank Statistic at End of Trial

Given Interim Log-Rank Statistics

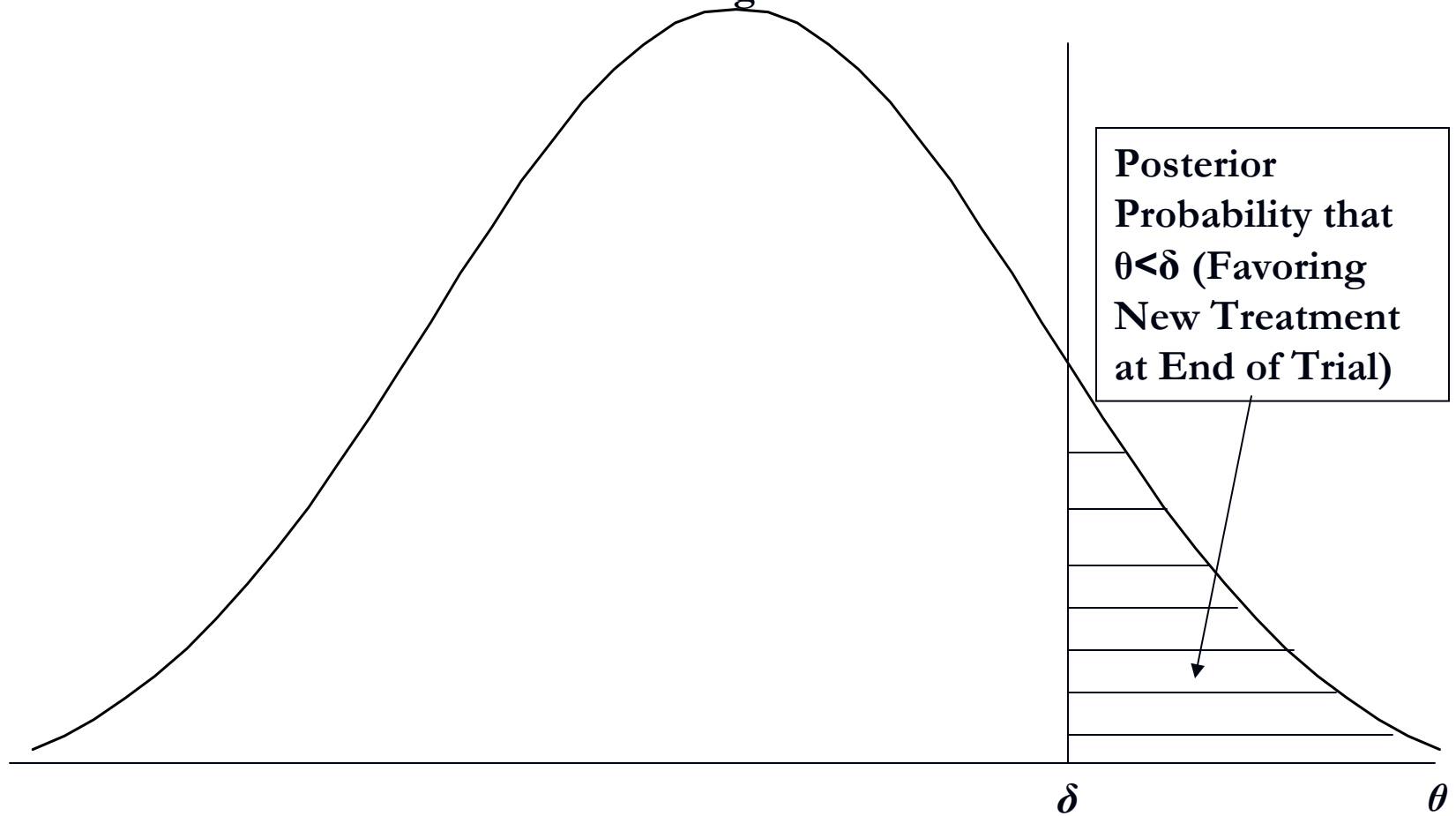




# “Pure” Bayesian Approach

Posterior Distribution of  $\theta$  at End of Trial

Given Interim Log-Rank Statistics



# Conclusions

- No approach is ‘optimal’ and any given futility stopping boundary can be derived from any of the usual approaches with appropriate specifications.
- Choice of “aggressive” or “conservative” futility approaches will depend partially on non-statistical considerations (toxicity of the treatments; type of ‘standard’ treatment; outcome measures; etc)