Novartis: Challenging to Accelerate Oncology New Drug Development

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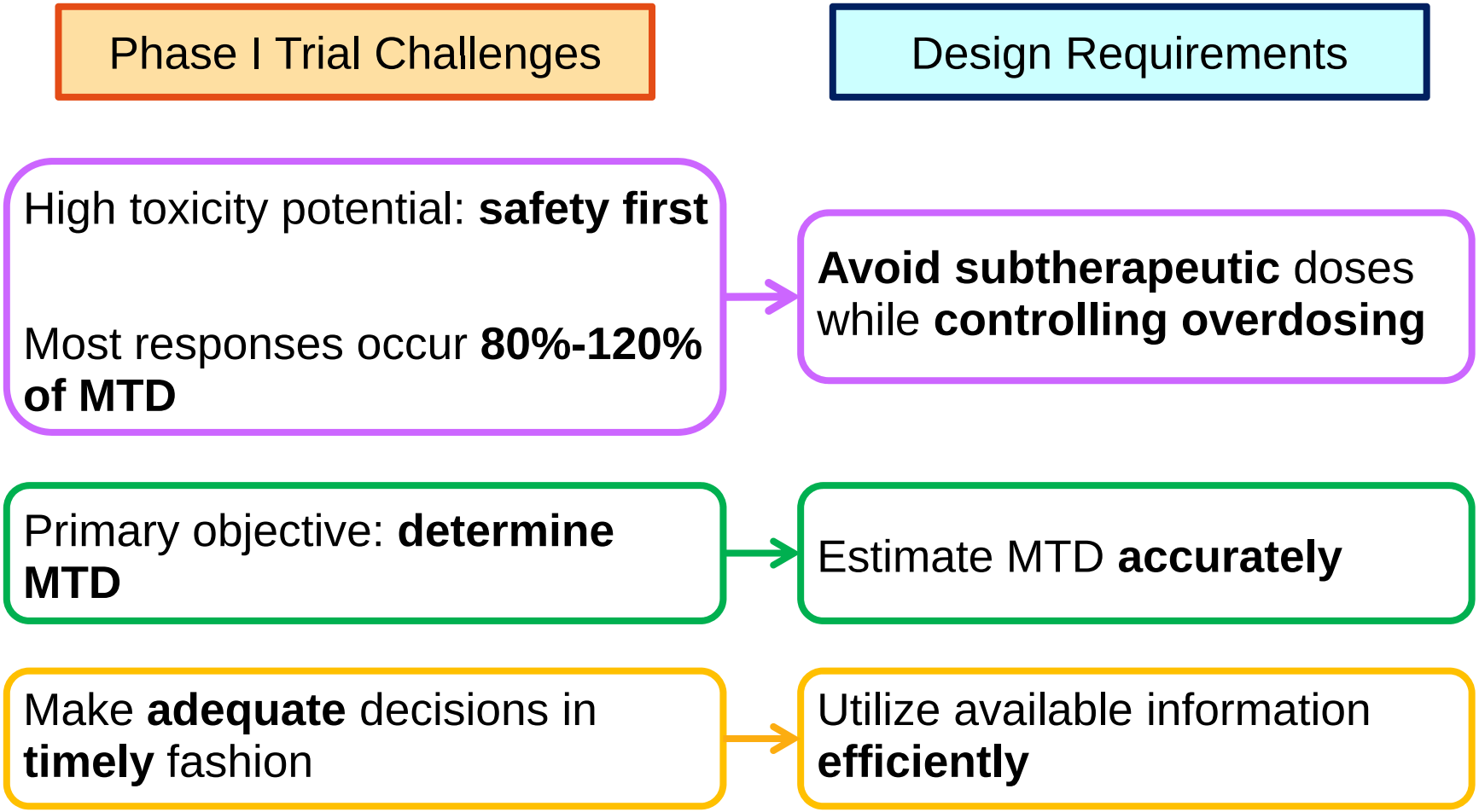
Bayesian Clinical Trials in Novartis Oncology

- Phase 1 study
  - To estimate the maximum tolerated dose (MTD)
  - Global (1998-): > 60 trials, Japan (2008-): 6 trials
- Phase 2 study
  - Early stopping by futility
  - >50 trials
- For Novartis oncology P1 studies, Bayesian trials are the global standard!

Outline

- Why do we conduct Bayesian Phase I Trials?
- How do we conduct Bayesian Phase I Trials?
- What benefits can Bayesian Design bring us to?

Challenges and Design Requirements in Oncology Phase I Trials



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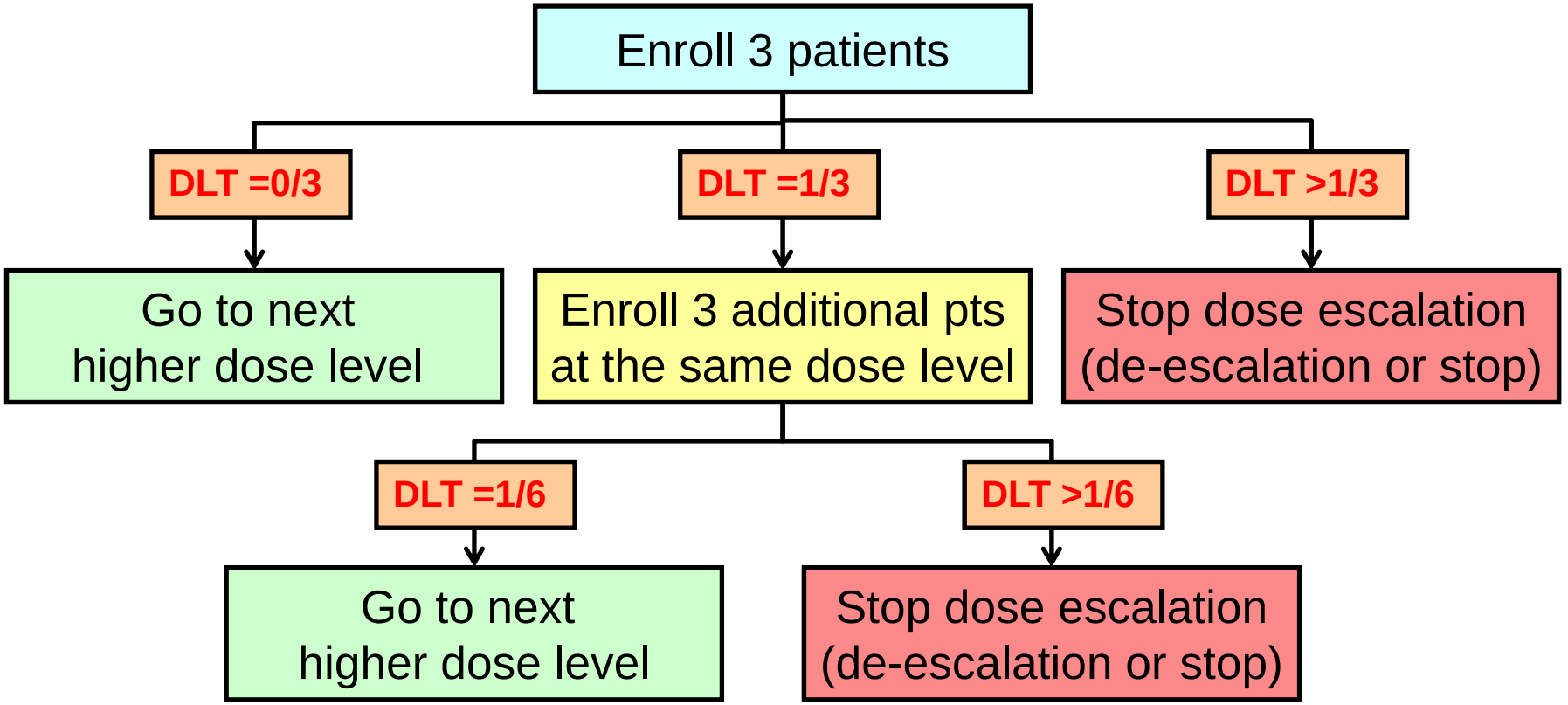
Traditional 3+3 Design



To determine the next dose, only **the number of DLT at the current cohort** is used.

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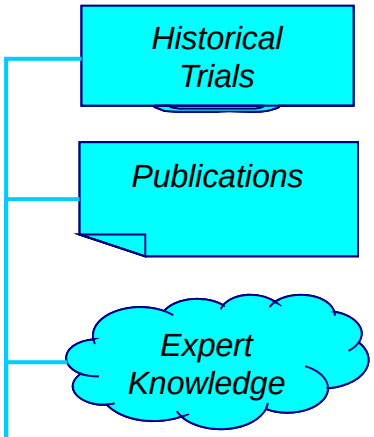
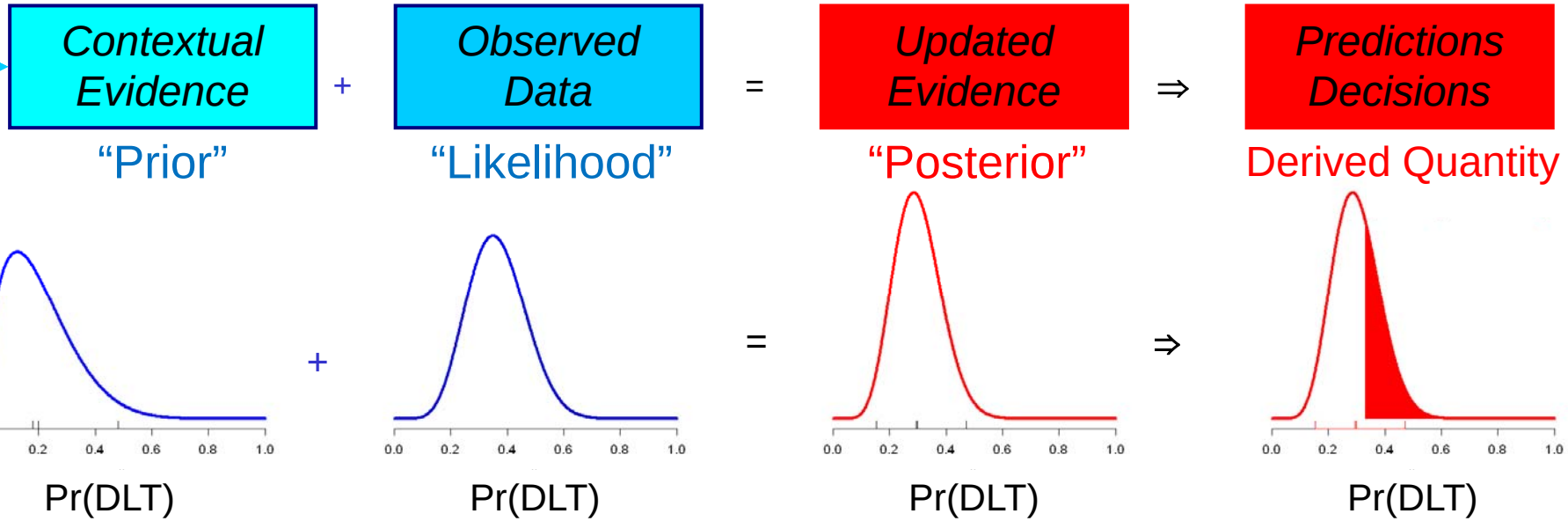
Bayesian Statistics



Advantages

- Different sources of information are combined probabilistically
-Accurate prediction can be obtained by putting together our historical knowledge and ongoing trial data



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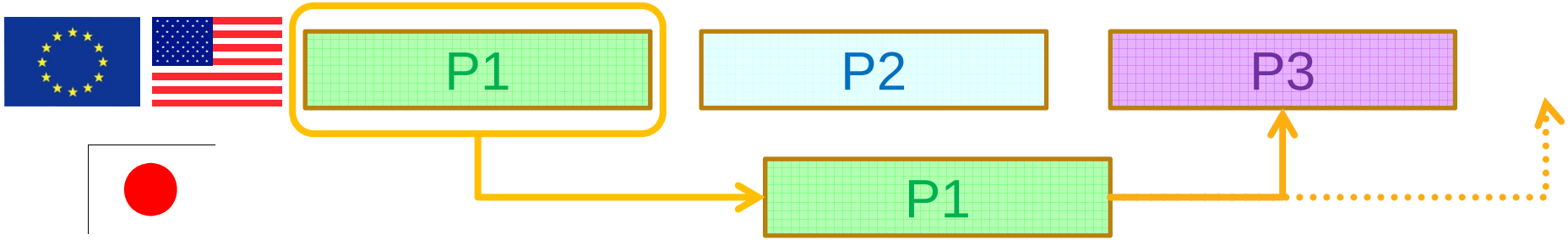
3+3 Design vs Bayesian Design

	3+3 Design	Bayesian Design
Usability	Easy - algorithm	More complex - model
Available information	•The number of DLT at current cohort	•Prior information •Ongoing trial data
Flexibility	Not flexible ▪ fixed cohort size at 3 ▪ fixed doses	Flexible ▪ adjustable cohort size ▪ unplanned doses
Accuracy of MTD estimation	Lower	Higher
Inference for true DLT rates	•Observed DLT rates	•Estimate DLT rates at each doses •Risks of DLT occurrence at each doses

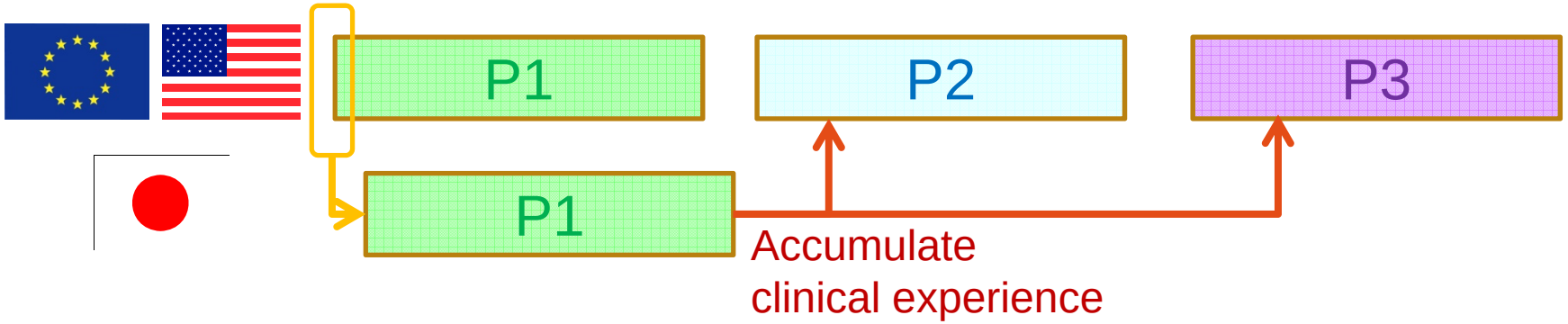
Bayesian Design can solve Challenges in Oncology Phase I Trials!

Challenge in Japan Development

<Delayed-Start Development>



<Simultaneous Development>



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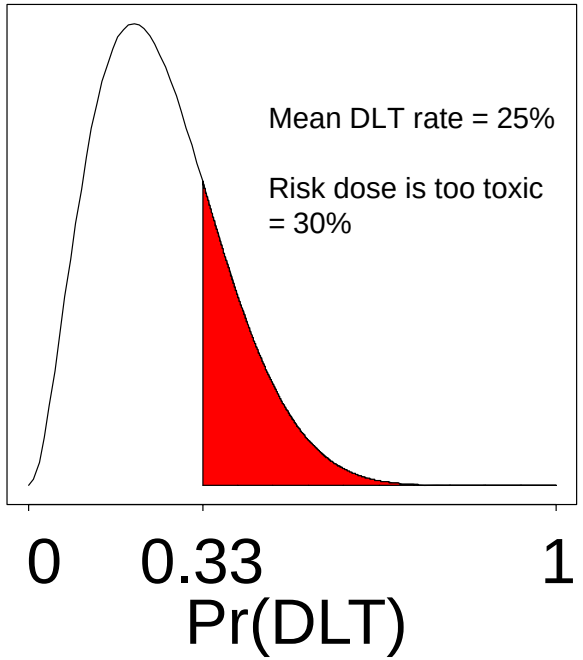
Novartis Bayesian Approach to Oncology Phase I Trials

- Assume dose-toxicity model
- Update probability of DLT rate at each dose by incorporating prior information (pre-clinical, human) and observed data into model
- Assess the risk of that the true DLT rate at each dose exceeds 33%, given all of our prior information and observed data



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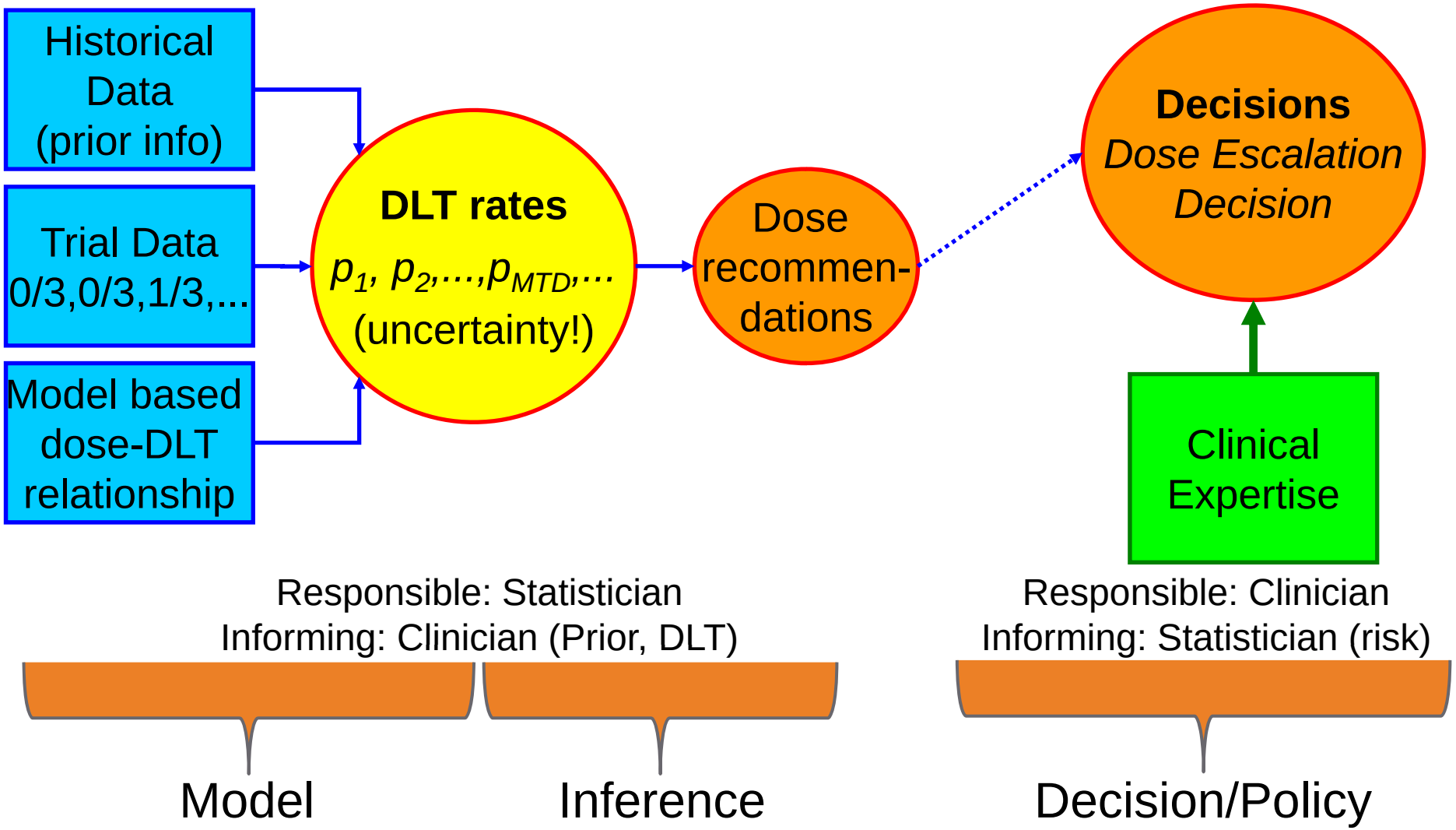
Clinically driven, statistically supported decisions



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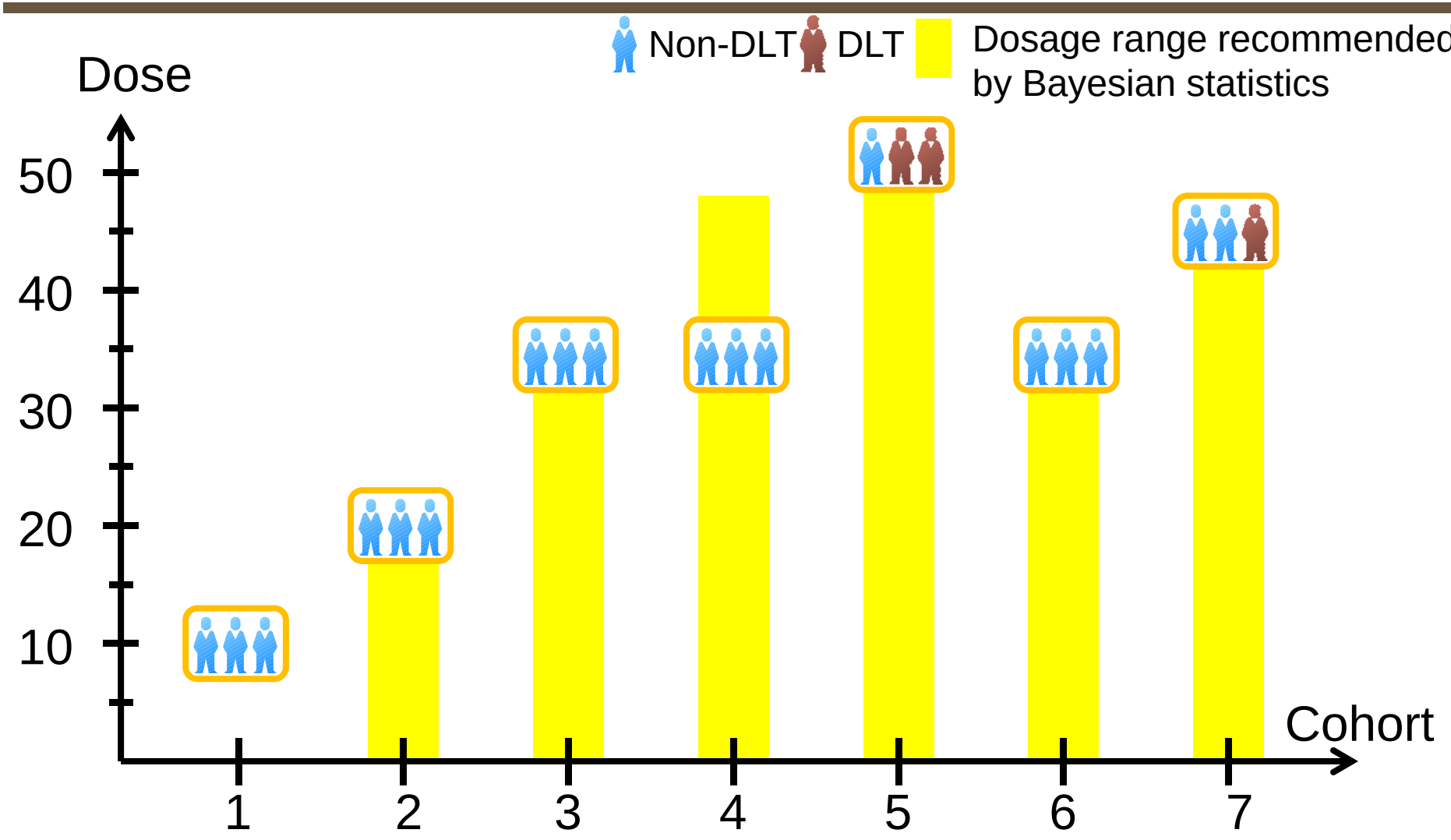
Example of Dose Escalation/De-escalation in Bayesian Oncology Phase I Trials



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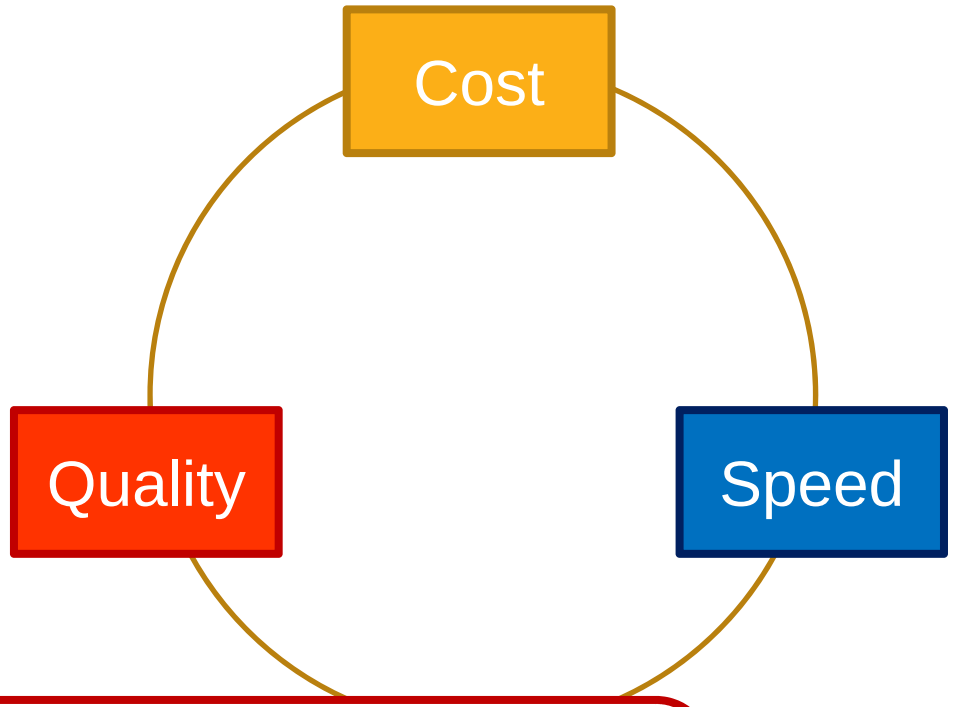
Benefits of Bayesian Oncology Phase I Trials



Accurately estimate MTD

- Utilize all relevant information
- Select next dose clinically
- Little-affected by DLT occurred by chance

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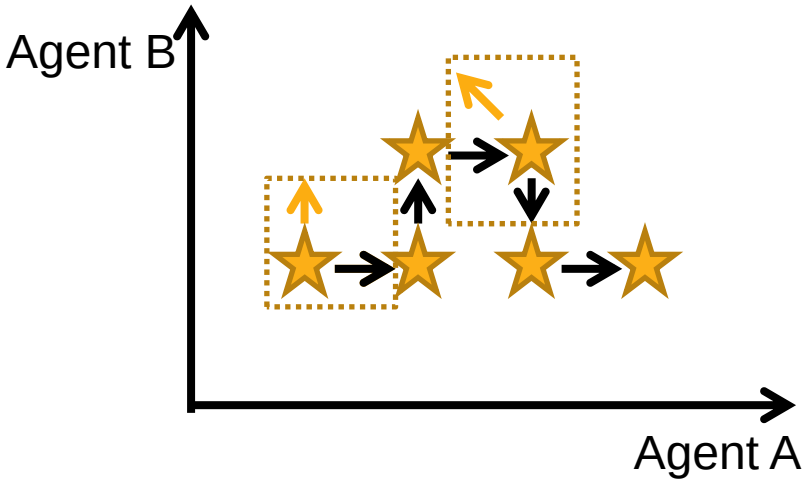
New Challenges

- Combination phase I study
  - Incorporate each historical SINGLE agent data into prior
  - Allow flexible dose escalation decisions clinically (dosage/agent)



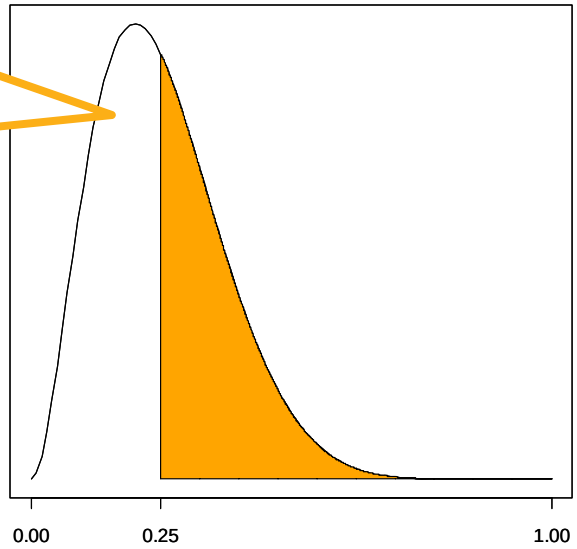
- Global/Asian phase I study
  - Estimate Global/Asian MTD considering the ethnic sensitivity in one trial

Example of Novartis Bayesian Approach to Oncology phase II Trials

Endpoint: ORR
Objective: to observe an ORR ≧ 25%

Prior Information + *Observed Data* = *Updated Evidence* → *Prediction*

Predict the "**probability of success**" at the end of the study
Pr(Final ORR≧25%|data)



Low → Stop the trial

Moderate → Continue the trial

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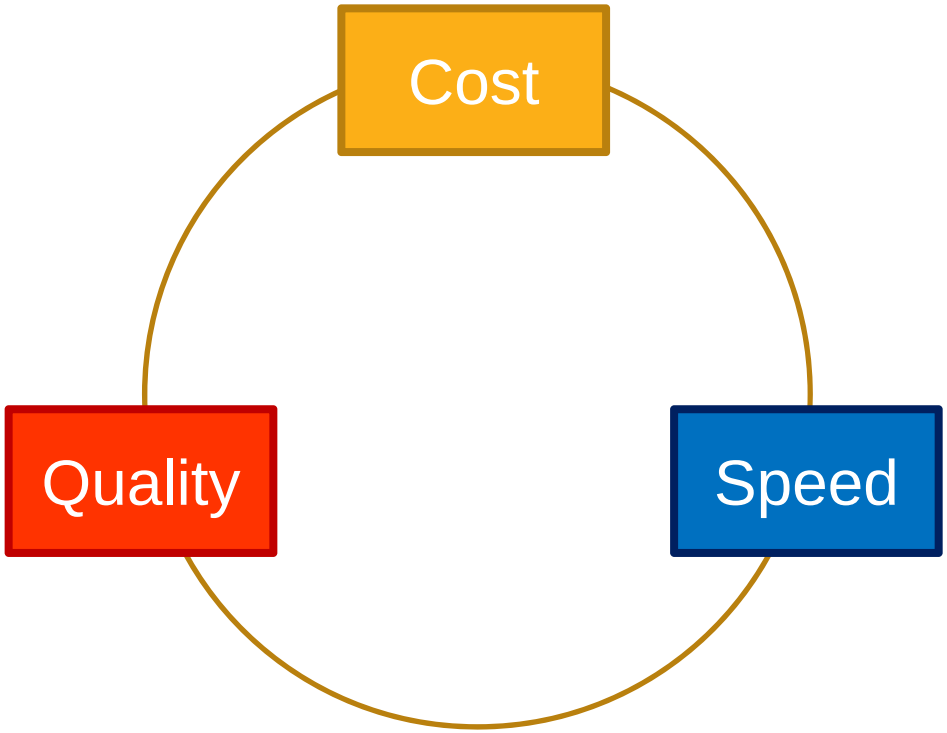
Expectation to Bayesian Trial Designs



Bayesian study design can maximize the quality of the new drug development!

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