Use of Conditional Assurance for Decision Making in Phase 1 Dose Escalation in Early Oncology

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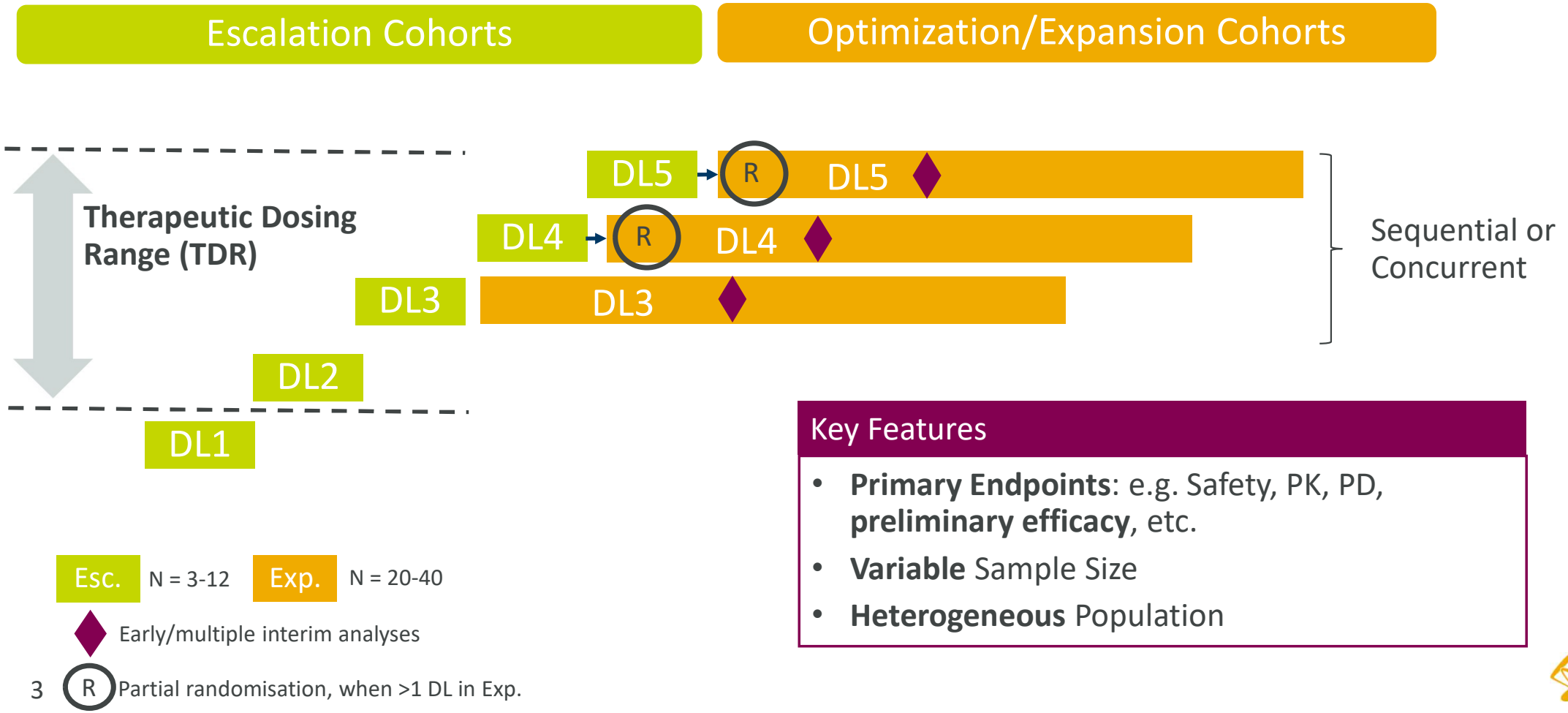
Early Oncology Two-Step Dose Optimisation Schematic



Key Features

- **Primary Endpoints**: e.g. Safety, PK, PD, **preliminary efficacy**, etc.
- **Variable** Sample Size
- **Heterogeneous** Population

Decision Gate to Consider Conditional Assurance of Expansion

Conditional Assurance

The **predictive probability** of **success** in optimisation or expansion cohorts conditional on the data observed during dose escalation

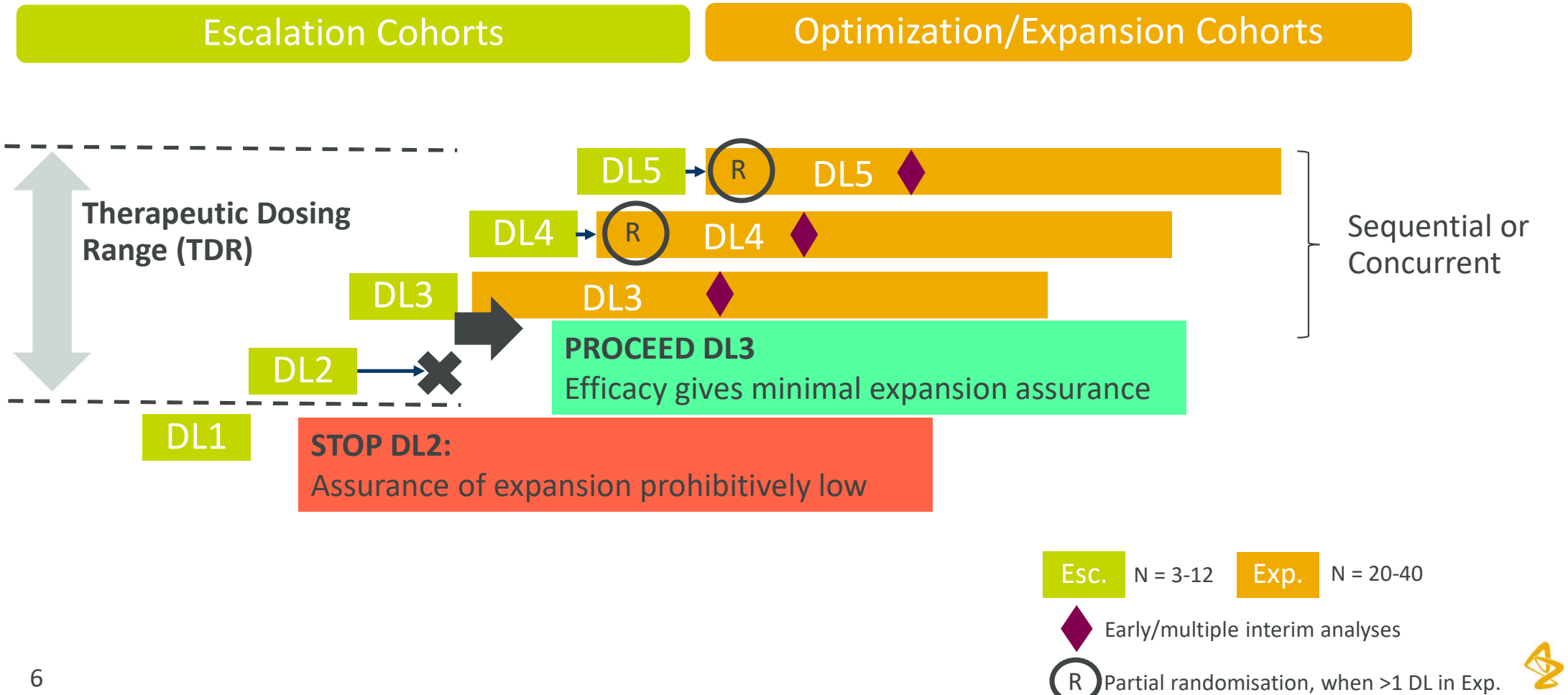
The Question it Answers

How much has the **emerging escalation data** increased or decreased chance of expansion success relative to what we believed before we started?

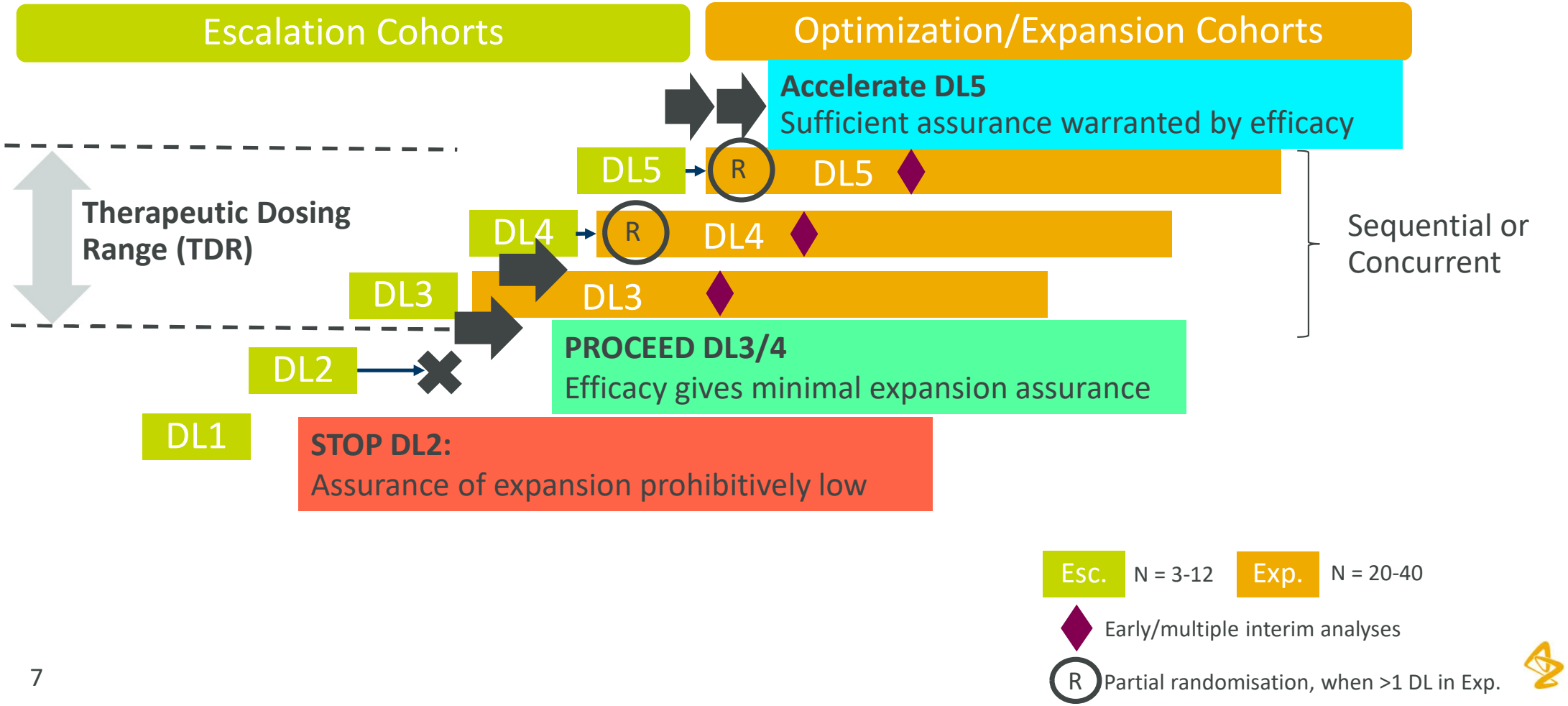
Opportunities Built on Consistency, Speed and De-risking

- ✓Consistent **quantitative** statistical thinking using assurance to quantify risk of inadequate efficacy and plan to de-risk accordingly
  - Estimate and **control risk** of 'false-stop' for a given dose level
- ✓Answers questions of **when and how**
  - Enables seamless expansion
  - Optional acceleration
- ✓**Flexible** in meeting project specific need

Enabling Seamless Clinical Development Plan



Enriching Clinical Development Plan via Opportunity of Early Acceleration



Efficacy Gatekeeper Complements Optimization Designs

Stage 1: Multi-dimensional data determines TDR in Escalation Cohorts

Safety & Tolerability	PK
PD	Efficacy

Designs to Consider:

Safety only: mTPI-2, CRM

Safety and PK and/or PD: DROID

Safety and Efficacy: BOIN12

STOP

Assurance of expansion prohibitively low

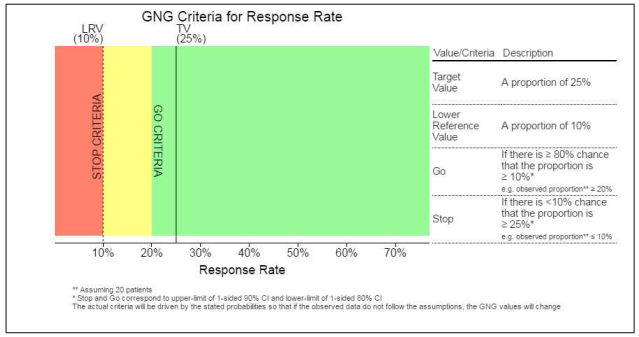
PROCEED

Minimum efficacy assurance threshold as gatekeeper

ACCELERATION

Sufficient assurance warranted by efficacy

Stage 2: Determine Optimal Dose in Optimization/Expansion Cohorts



Designs to Consider:

Lalonde Go-NoGo

Continuous Monitoring

Assurance, BOIN12, DROID

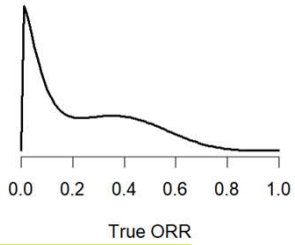
TV = 0.4, LRV = 0.15, n2 = 30

Expansion Assurance And Conditional Assurance

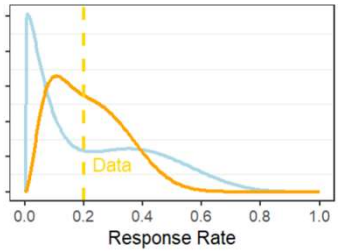
Escalation Phase

Expansion phase

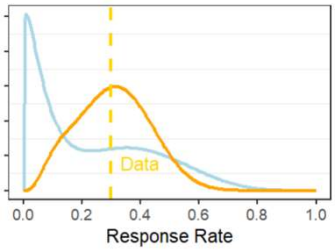
No Escalation phase data



= 2/10 responders



= 3/10 responders



Go Assurance = 37.7 %

Minimum Conditional Go Assurance = 30.0 %

Minimum Conditional Go Assurance = 54.4 %

7.7 %

Minimum Derisked Assurance

16.7%

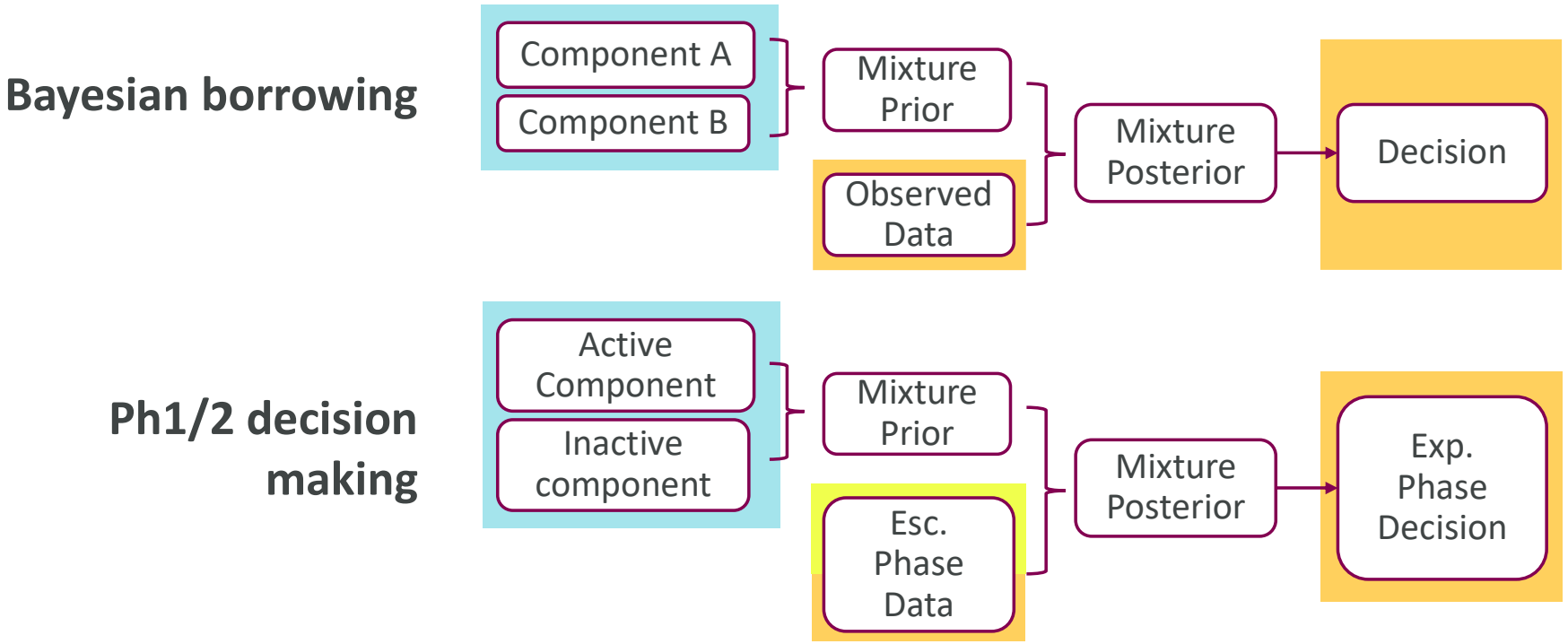
Minimum Derisked Assurance

Use Bayesian Borrowing to Inform Minimum Conditional Assurance

External data

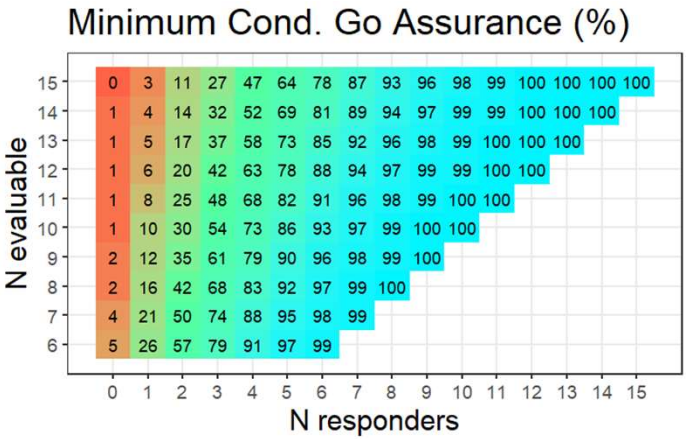
A homogenous population

A heterogenous population



TV = 0.4, LRV = 0.15, n2 = 30

Example: Dynamic Decision Making



STOP

A < 10% assurance to meet Expansion Go or Consider

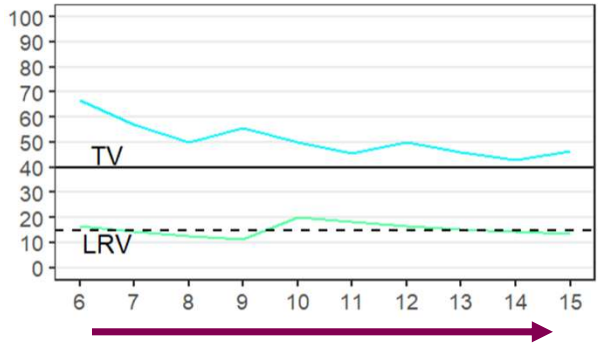
PROCEED

A ≥ 10% assurance to meet Expansion Go or Consider

ACCELERATION

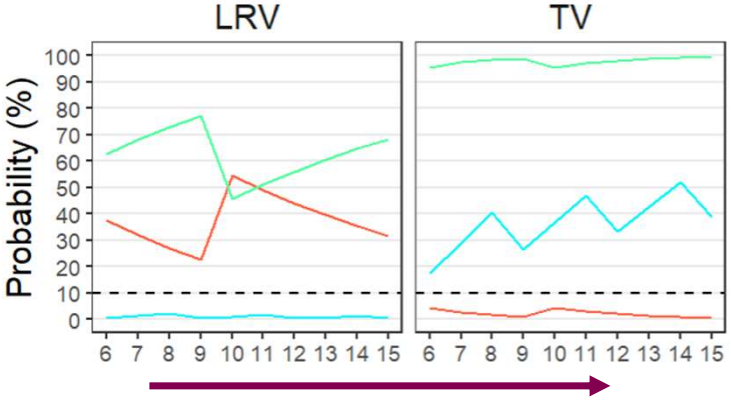
A ≥ 80% assurance to meet Expansion Go

Decision Criteria



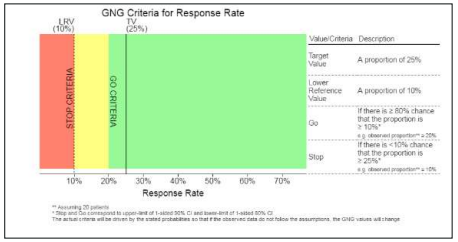
Emerging Data: N Patients

% of Outcome Given True Drug Effects

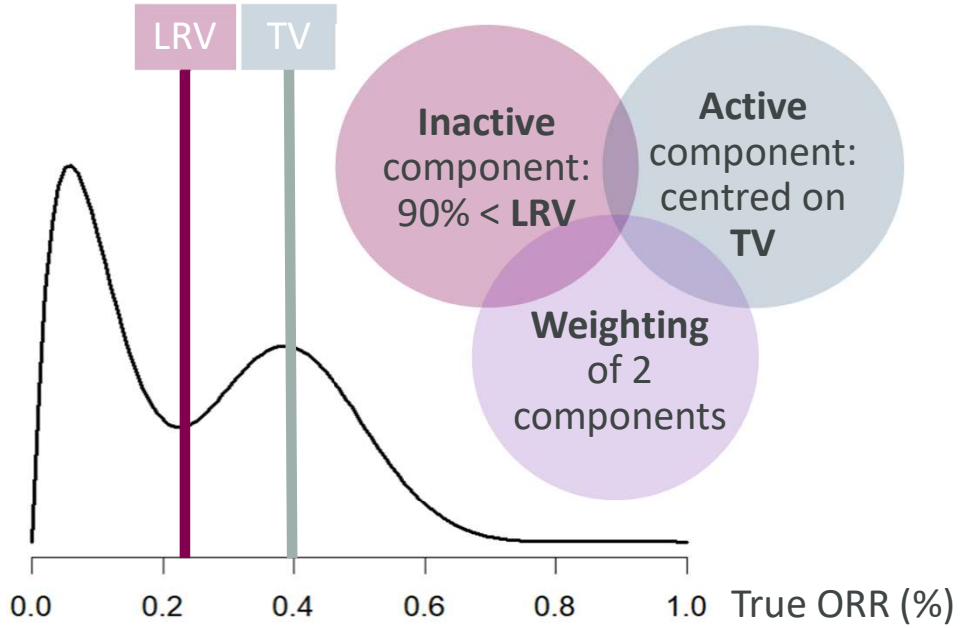


Emerging Data: N Patients

Bayesian Mixture Design Prior: Rule Of Thumb



Components



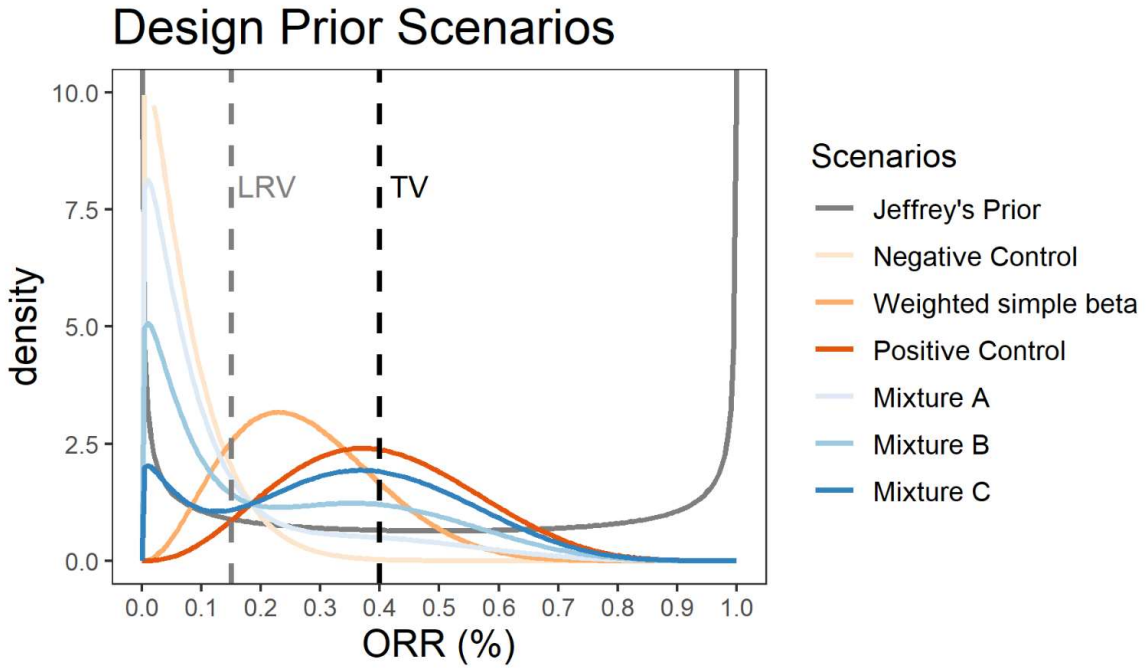
Points of consideration
• Pre-clinical evidence: PD-efficacy translation
• External evidence: MoA/Treatment modality
• Population

1. Calibrates Ph1 expansion conditional assurance given underlying uncertainty in early development
2. Provides a framework to estimate de-risking potential of upcoming studies
3. Offers robust efficacy cut-offs
4. Prevents over-reaction to small emerging datasets

MoA: Mechanisms of Actions; PD: Pharmacodynamics

TV = 0.4, LRV = 0.15, n2 = 30

A Bayesian Mixture Design Prior Enables Calibrating Ph1 Expansion Conditional Assurance

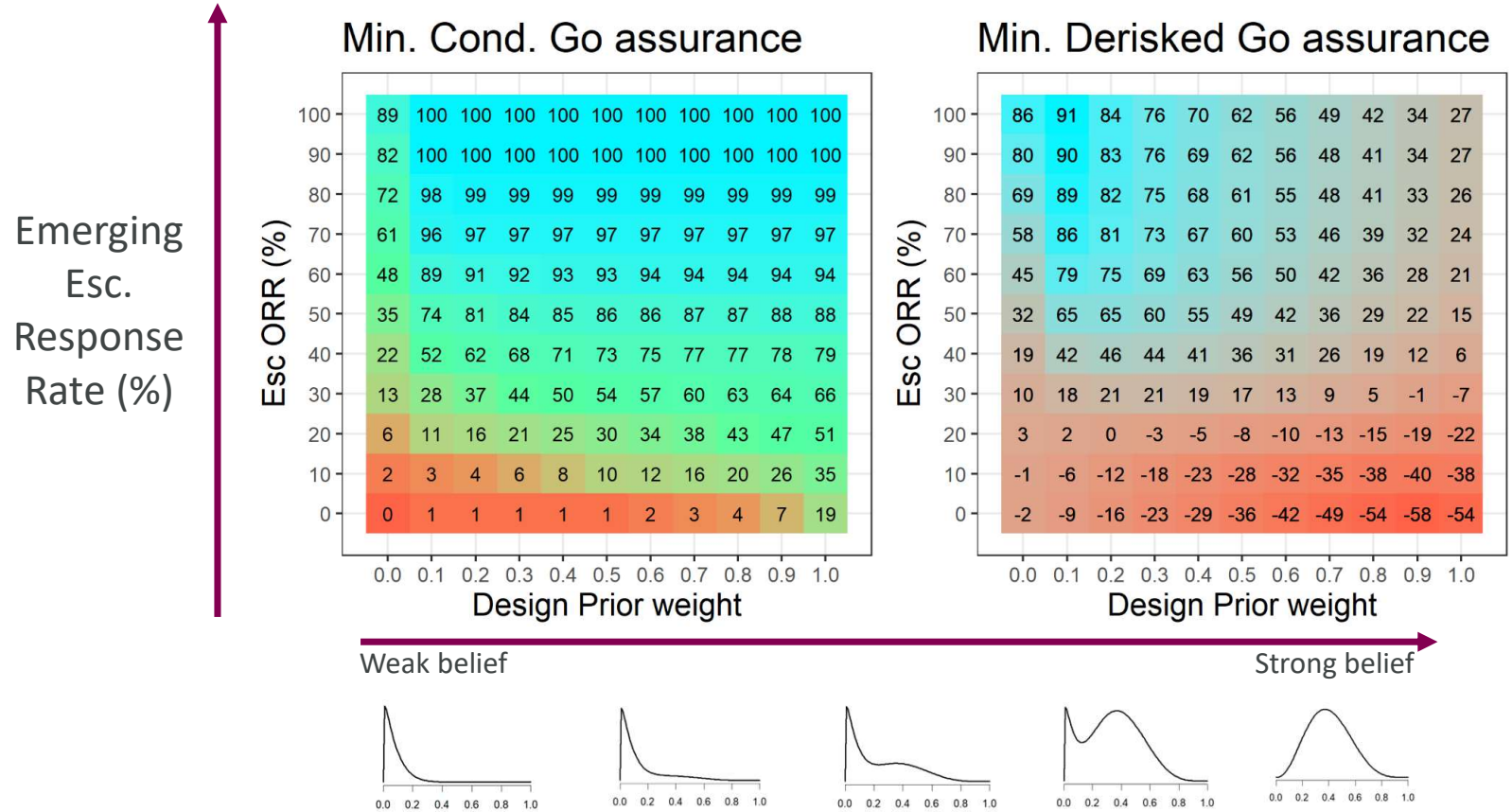


Scenario	ESS *	Baseline Go assurance	
Jeffreys prior	1	64.2%	
Neg. control	15	2.4%	Simple Beta Prior
Weighted simple beta distribution	12	44.1%	Simple Beta Prior
Pos. control	9	72.4%	Simple Beta Prior
Mixture prior A	20	**16.4%**	Mixture Prior
Mixture prior B	13	**37.7%**	Mixture Prior
Mixture prior C	9	**58.3%**	Mixture Prior

* ESS (Effective Sample Size): FDA recommend expected local-information-ratio (ELIR) method

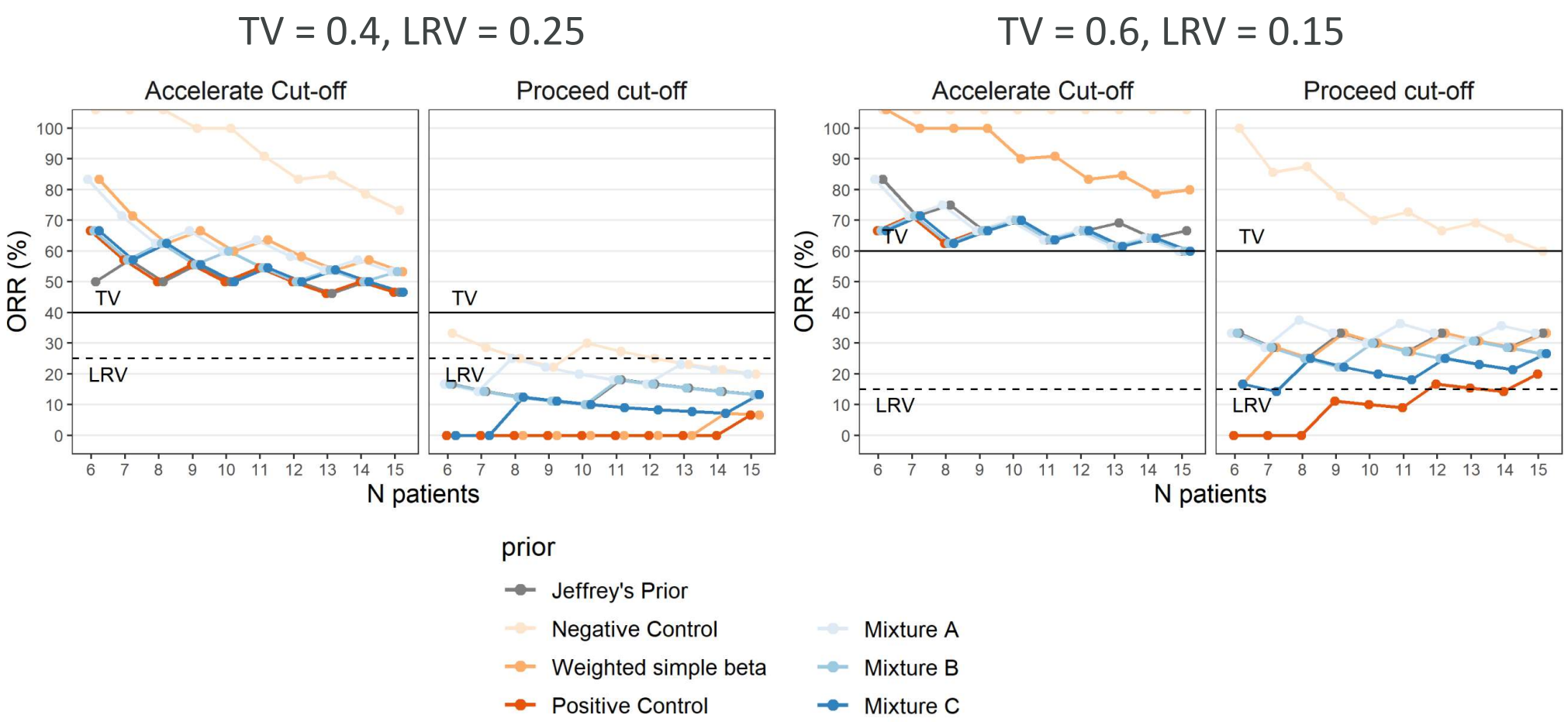
TV = 0.4, LRV = 0.15, n1 = 10, n2 = 30

A Bayesian Mixture Design Prior Provides A Framework To Estimate De-risking Potential Of Upcoming Studies



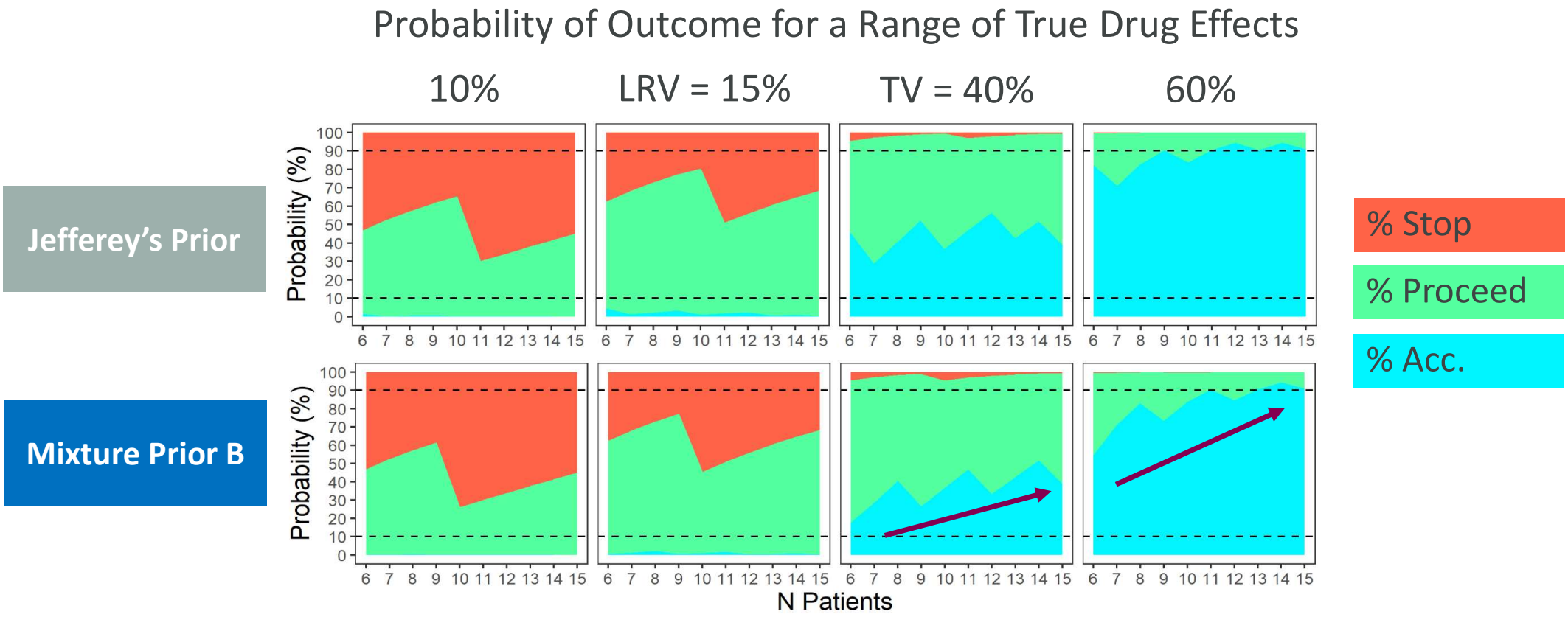
n2 = 30, proceed cut-off 10%, acceleration cut-off 80%

A Bayesian Mixture Design Prior Offers Robust Efficacy Cut-offs



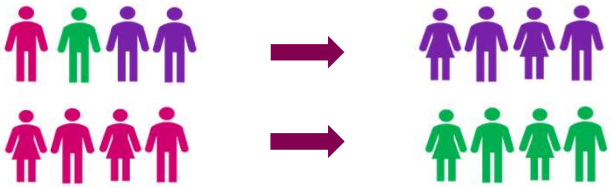
TV = 0.4, LRV = 0.15, n2 = 30, proceed cut-off 10%, acceleration cut-off 80%

A Bayesian Mixture Design Prior Prevents Over-reaction To Small Emerging Datasets



Further Opportunities

Different Population across Esc. and Exp. Phase

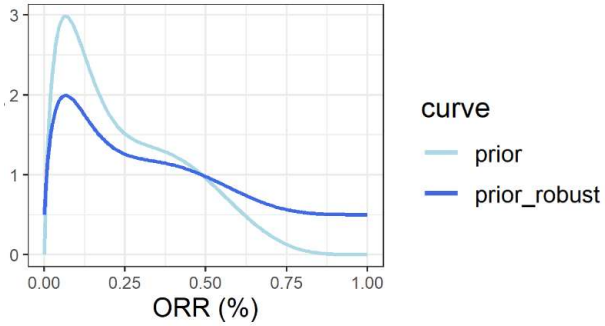


? How are Esc./Exp. population **selected**

? **Amount** of evidence

➢ **Adjust** prior components

➢ **Robustify** prior



Different Decision-Making Endpoints across Esc. and Exp. Phase

RECIST ORR

ctDNA

PSA50

PD biomarker

➢ **Types** of endpoints

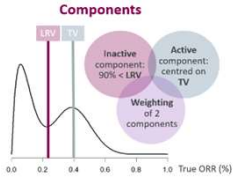
➢ **Correlation** between the surrogate outcome and the clinically meaningful outcome

➢ Clinical relevance of a **composite** endpoint

Take Home Messages

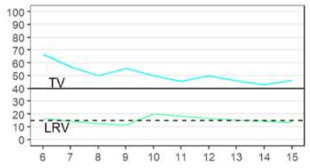
Quantitative Decision Framework

- Bayesian Borrowing
- Mixture Prior



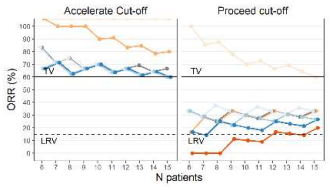
Dynamic Decision Making

- When
- How

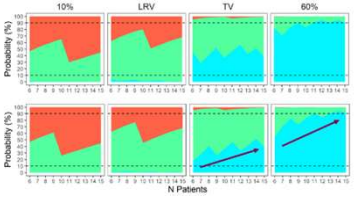


Robust Framework

- Decision criteria
- O/C



Controlling False Stop and False Acceleration



Flexibility

- Design Prior
- Threshold
- Different Population/ Endpoints

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- Kopp-Schneider, A., Calderazzo, S., & Wiesenfarth, M. (2020). **Power gains by using external information in clinical trials are typically not possible when requiring strict type I error control.** Biometrical Journal, 62(2), 361-374.

Back-ups

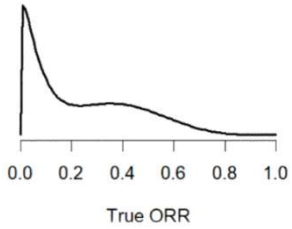
TV = 0.4, LRV = 0.15, n2 = 30

Expansion Assurance And Conditional Assurance

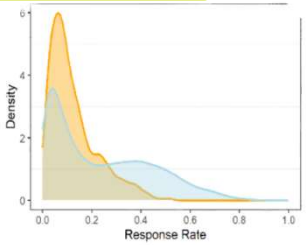
Escalation Phase

Expansion phase

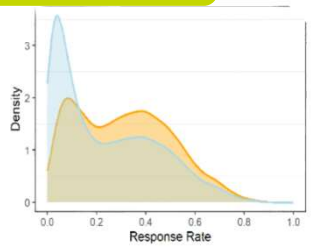
No Escalation phase data



= 2/10 responders



>= 2/10 responders



Go Assurance = 37.7 %

Minimum Conditional Go Assurance = 30.0 %

7.7 %

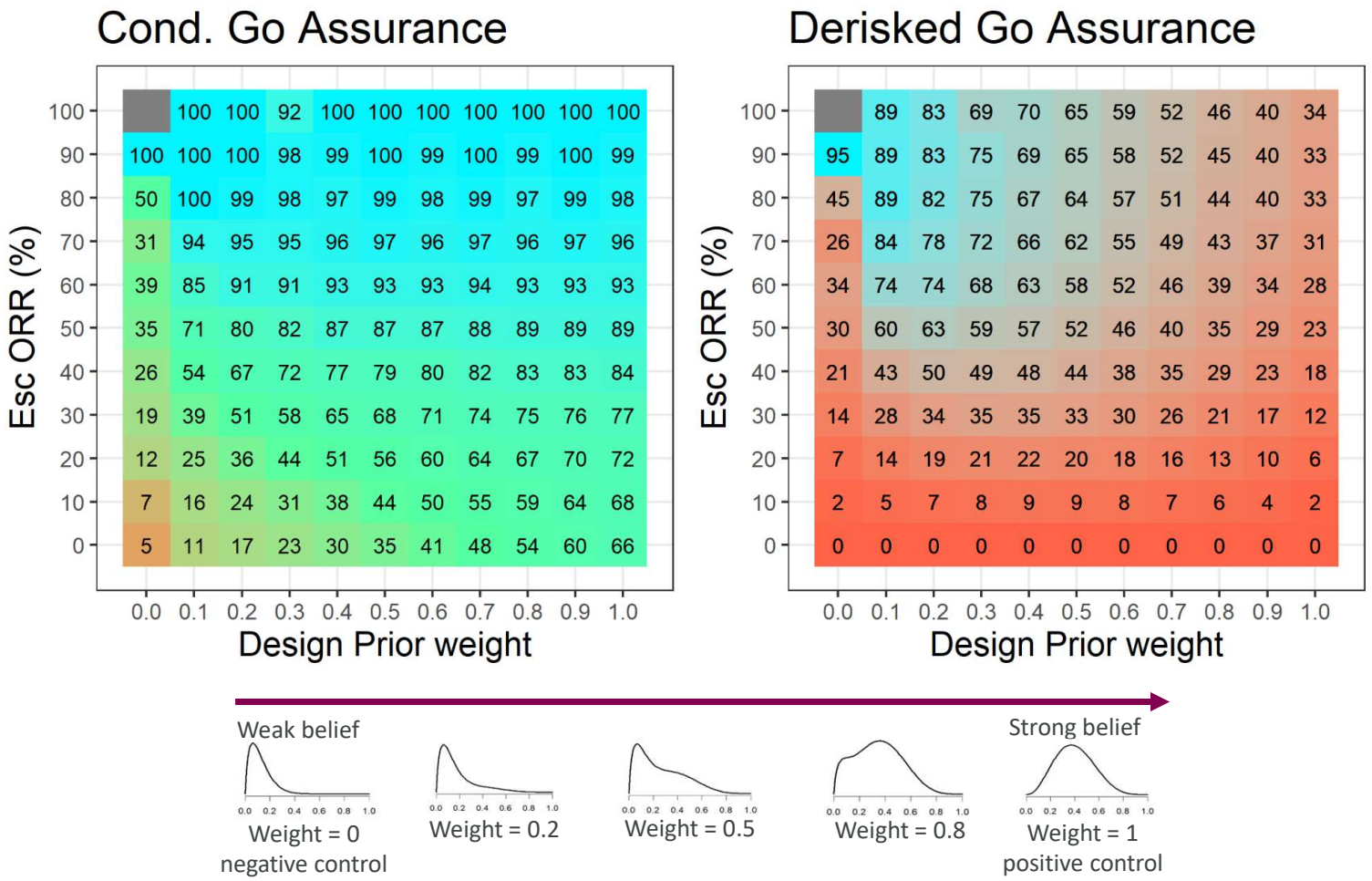
Minimum Derisked Assurance

29.2 %

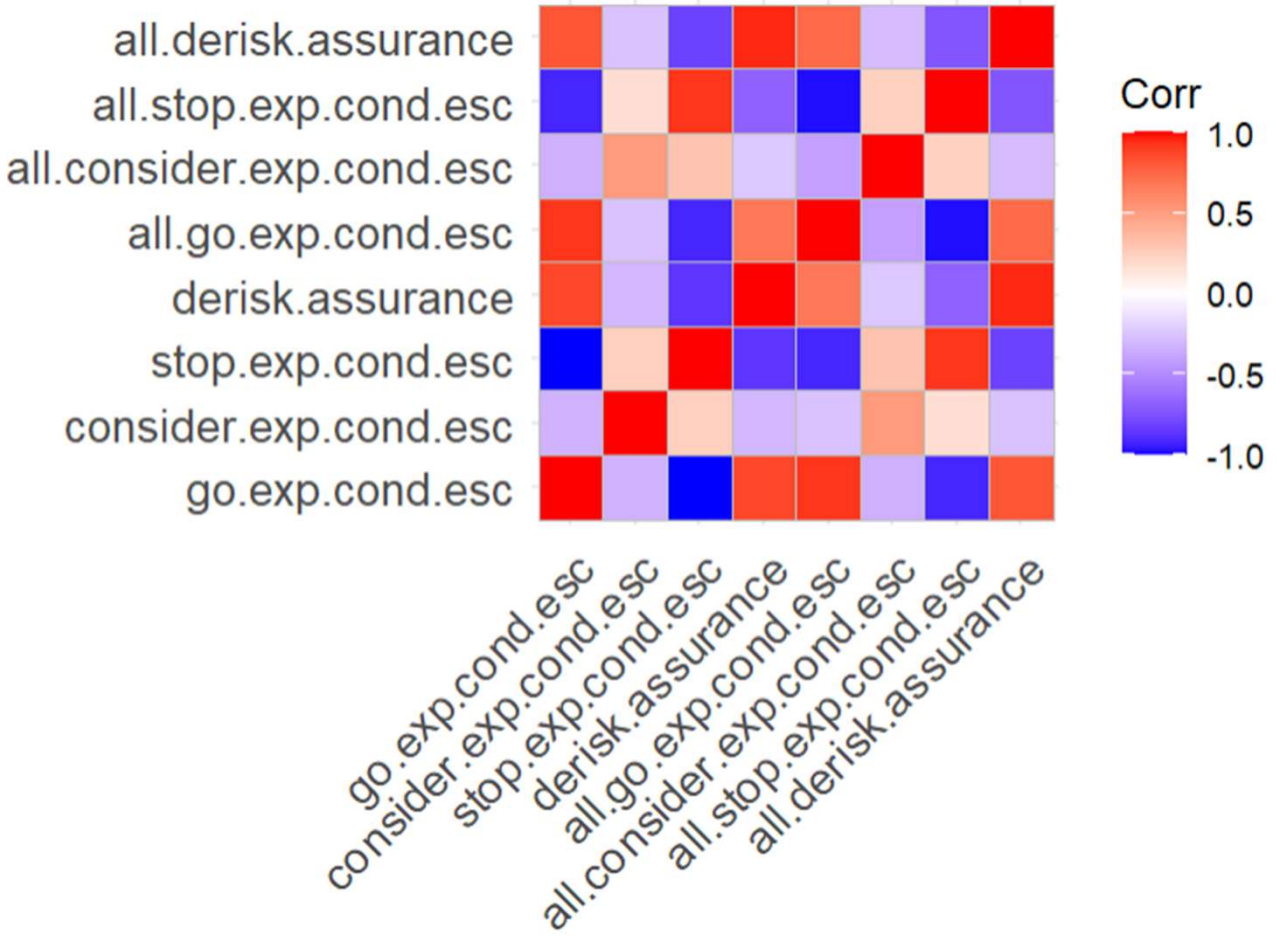
Derisked Assurance

Conditional Go Assurance = 66. %

Overall Cond. Assurance



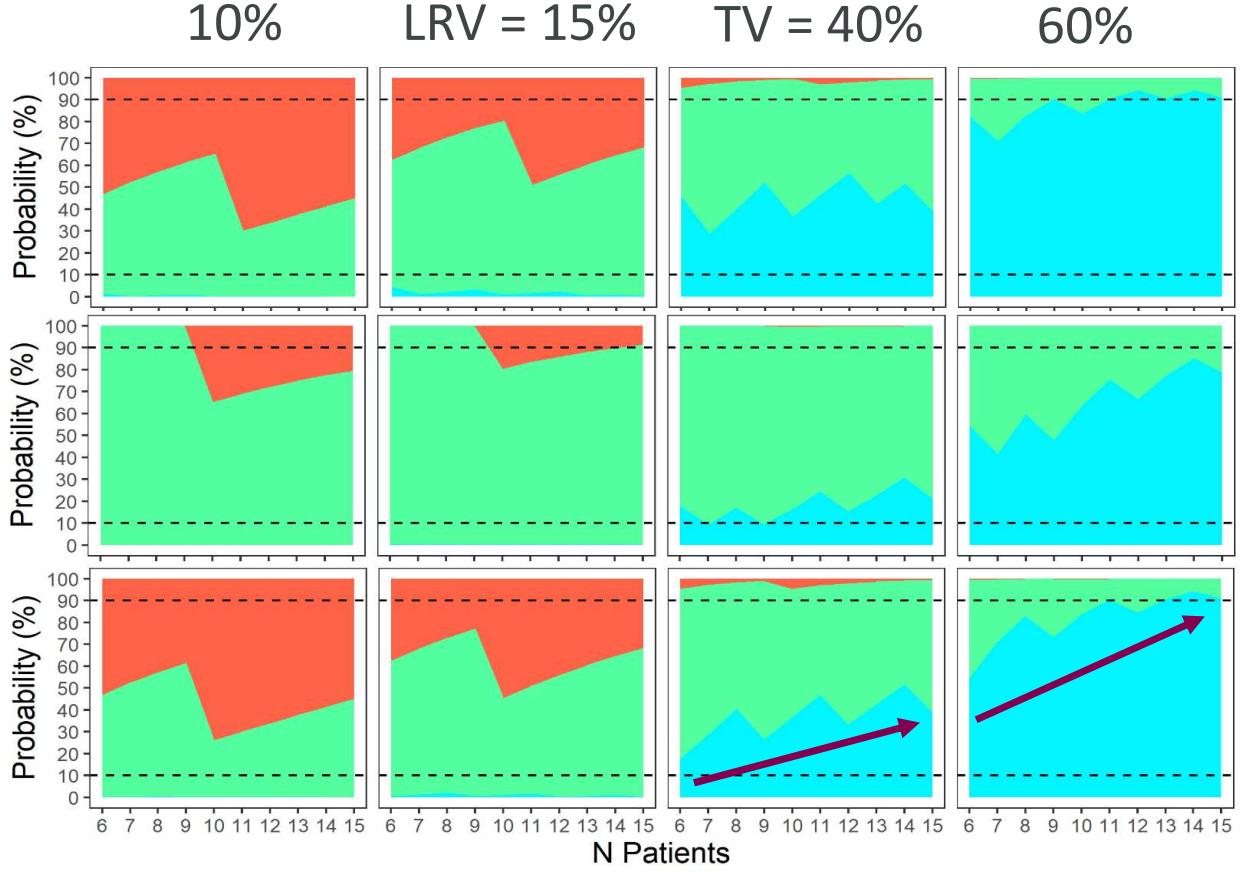
Min. VS Cond. Assurance



TV = 0.4, LRV = 0.15, n2 = 30, proceed cut-off 10%, acceleration cut-off 80%

A Bayesian Mixture Design Prior Prevents Over-reaction To Small Emerging Datasets

Probability of Outcome for a Range of True Drug Effects



Jefferey's Prior

Simple Weighted Beta

Mixture Prior B

Different Population across Esc. and Exp. Phase

Escalation Cohorts → **Expansion Cohorts**

Broad AST → Specific Tumour Type

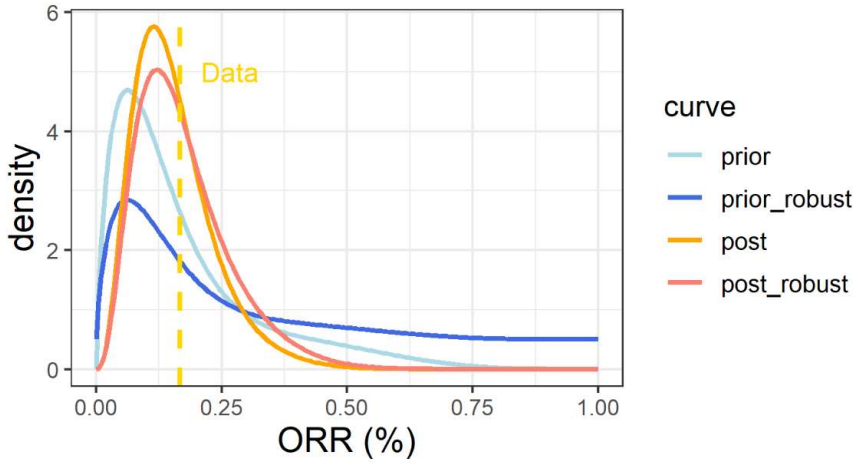
Tumour Type A → Tumour Type B

Points of consideration

- How are Esc./Exp. population selected
- Amount of evidence

Methods to consider

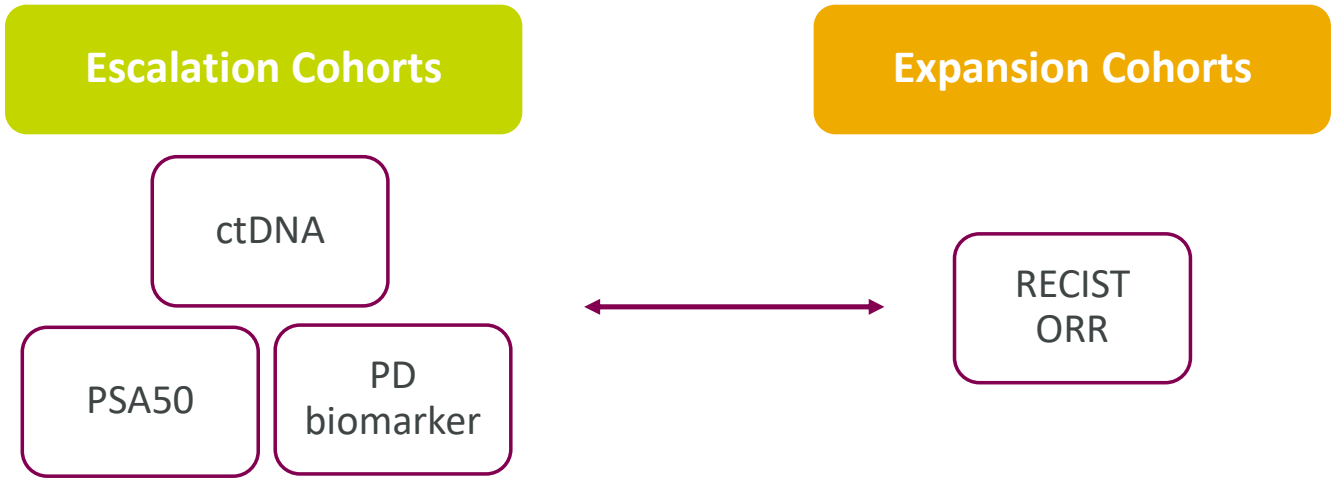
- Adjust prior components: weight, ESS, etc.
- Robustify prior



e.g. N = 12, R = 2

AST: Advanced Solid Tumour; ESS: Effective Sample Size

Different Decision-Making Endpoints across Esc. and Exp. Phase



Points of consideration

• Types of endpoints: binary/continuous, etc.
• Correlation between the surrogate outcome and the clinically meaningful outcome
  • Positive/Negative predictive value
  • Sensitivity/Specificity
• Clinical relevance of a composite endpoint

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