Bayesian Adaptive Design for a Practice-Changing Platform Trial in a Rare Paediatric Cancer: The Glo-BNHL Trial

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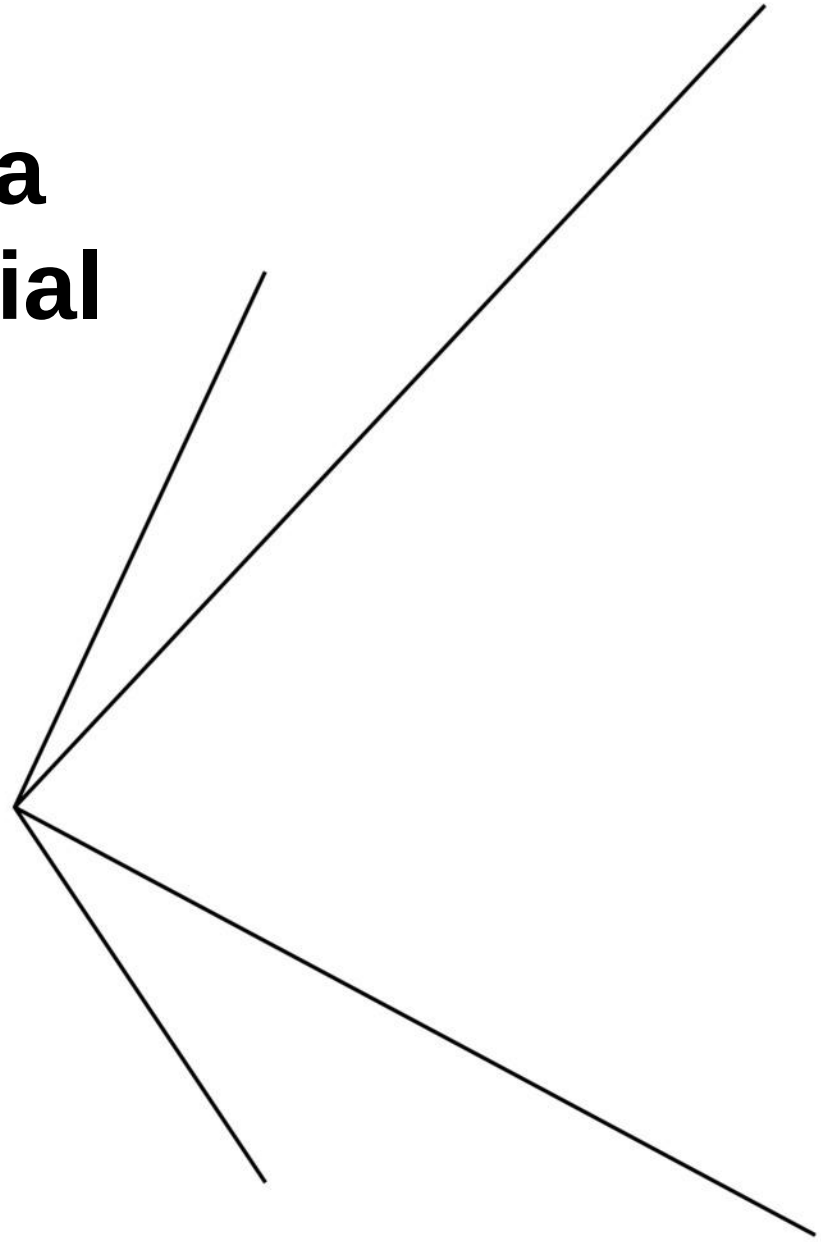

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GIO-BNHL

A Global Study of Novel Agents in Paediatric and Adolescent Relapsed and Refractory B-cell Non-Hodgkin Lymphoma (B-NHL)

Chief Investigator: Professor Amos Burke
Lead Biostatistician: Professor Lucinda Billingham
Trial Biostatisticians: Shanna Maycock, Jiayi Wang
Sponsor: University of Birmingham
CTU: Cancer Research UK Clinical Trials Unit

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CHILDREN'S ONCOLOGY GROUP

Innovative Therapies for Children with Cancer ITCC European Consortium

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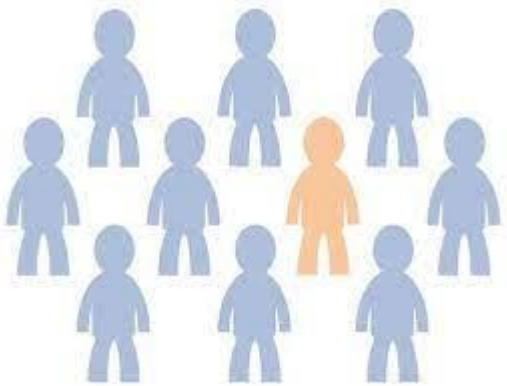
The Clinical Need for the Trial

- Population: Relapsed/refractory mature B-NHL
  - heterogeneous: histology and prior therapies received
- Estimated that ~30 patients per year could realistically be recruited to trials from this population globally (Europe, North America and Australasia)
- Rare population with a number of promising novel agents to be tested
- Trials should limit the exposure of children, adolescents and young adults to potentially harmful and/or ineffective therapies



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INNOVATION FOR CHILDREN AND ADOLESCENTS WITH CANCER

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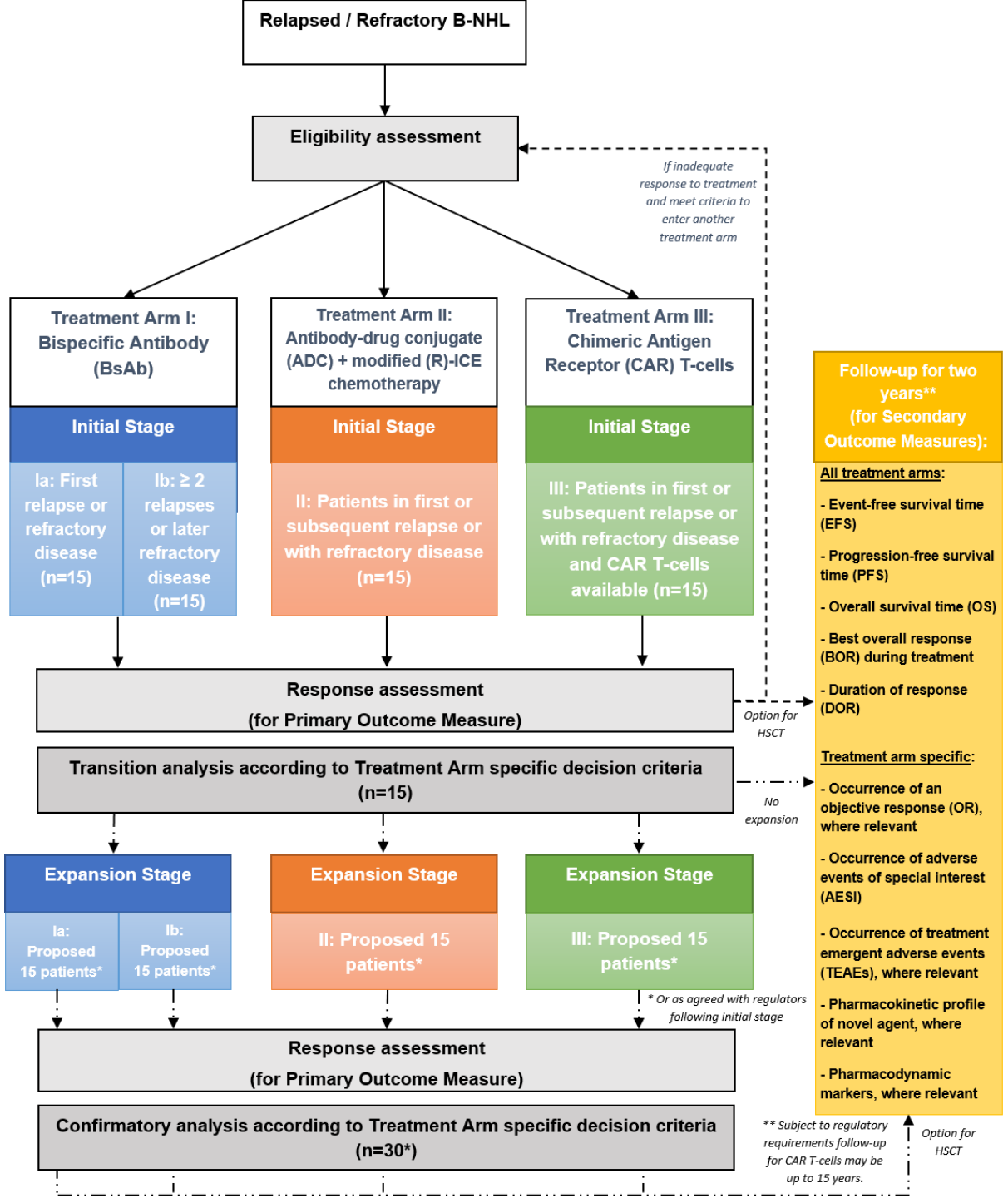
The Platform Trial Design

- 3 treatment arms (4 cohorts) being independently evaluated
- Expanding to include further treatment arms
- No control arms – evaluation based on single arm designs
- Overarching two-stage design common to all treatment arms but with some treatment arm specific criteria



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Trial Design: Treatment Arm Specific Criteria

	Treatment Arm Ia	Treatment Arm Ib	Treatment Arm II	Treatment Arm III
Population	1st Relapse / refractory B-NHL	B-NHL in >1st relapse	B-NHL in 1st or higher relapse or refractory disease	Insufficient response from prior relapse therapy
Intervention	BsAb	BsAb	ADC + R-ICE	CAR T
Primary outcome measure	Objective Response (OR)	Objective Response (OR)	Complete Response (CR) following max 3 cycles	Objective Response (OR)
Estimand	OR rate	OR rate	CR rate	OR rate
Clinically relevant critical value	40%	10%	20%	10%

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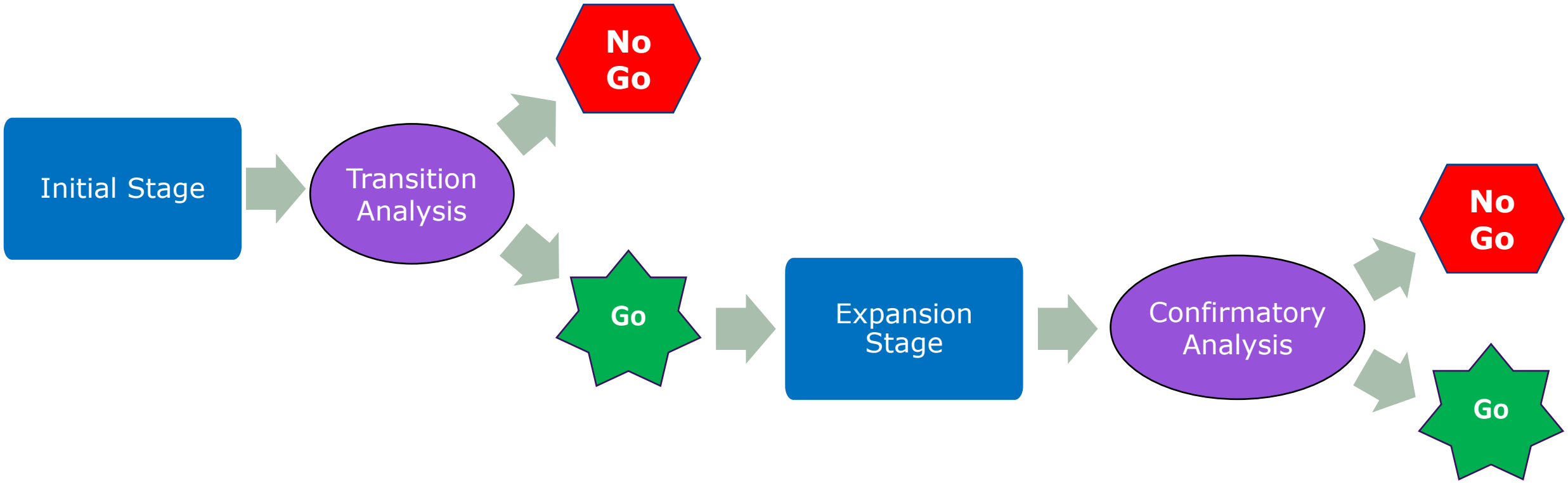
Decision Analysis Timeline



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Statistical Analysis Plan

- **Bayesian beta-binomial conjugate analysis**
  - Binomial likelihood: r responses / n patients
  - Beta prior distribution: beta(a,b)
    - Minimally informative: beta(1,1)
  - Beta posterior distribution: **beta(a+r, b+n-r)**
- Estimation from posterior probability distribution:
  - Response rate (median) and 95% credible intervals
- Decision-making based on posterior probabilities:
  - Transition analysis (N=15):
    if p(True response rate > Target) > 0.80 then GO
  - Confirmatory analysis (N=30):
    if p(True response rate > Target) > 0.95 then GO
- Simple approach due to small numbers of patients

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Transition Analysis Examples: Scenario 1

Treatment Arm II

Primary outcome: Complete Response (CR)
Target response rate: 20%

Data from Initial Stage

Responses: 3 / 15

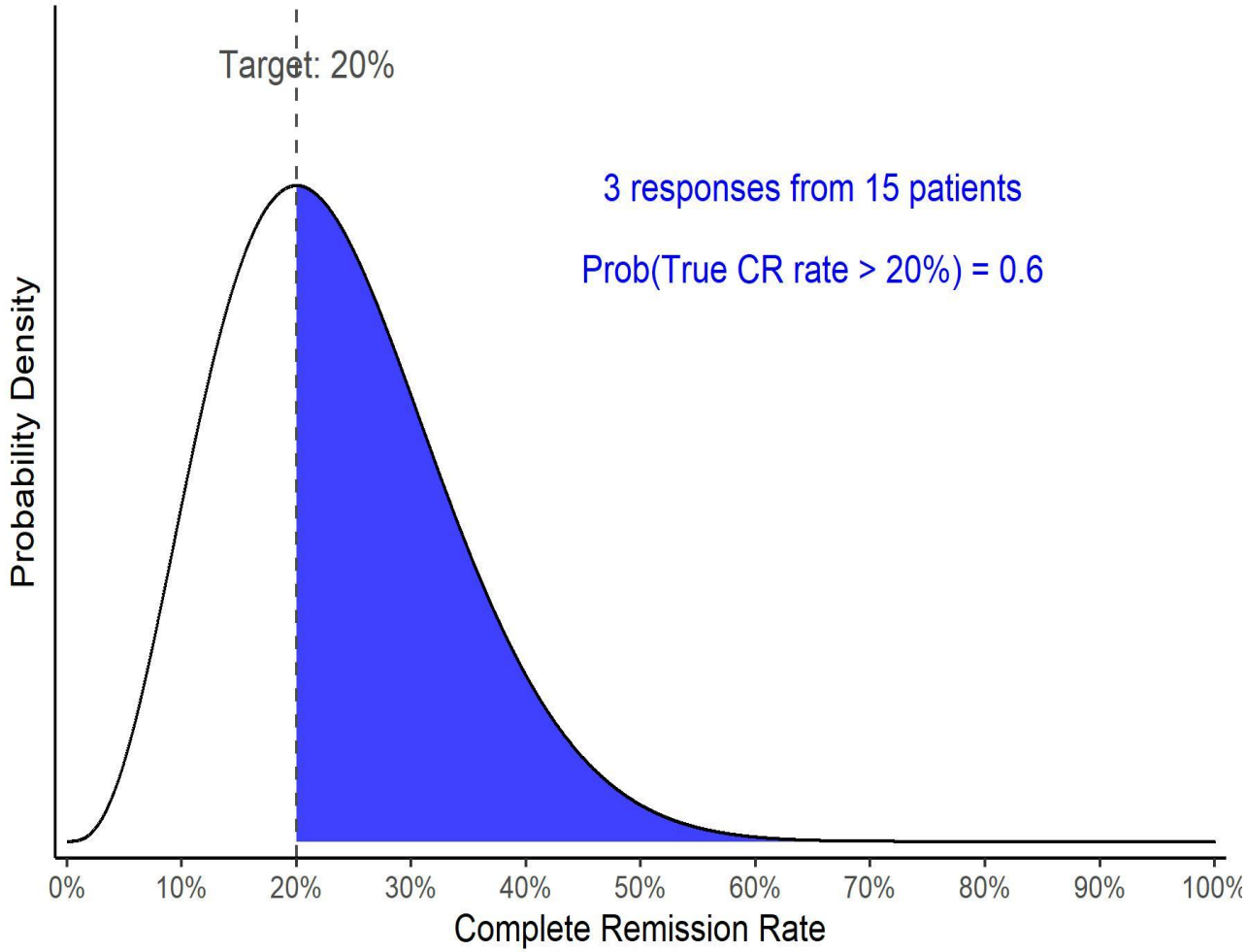
Observed CR rate = 20%

Bayesian estimate of true CR rate = 22.5%

95%CrI: (7%, 46%)

P(True CR rate > 20%) = 0.60

No Go



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Transition Analysis Examples: Scenario 2

Treatment Arm II

Primary outcome: Complete Response (CR)
Target response rate: 20%

Data from Initial Stage

Responses: 6 / 15

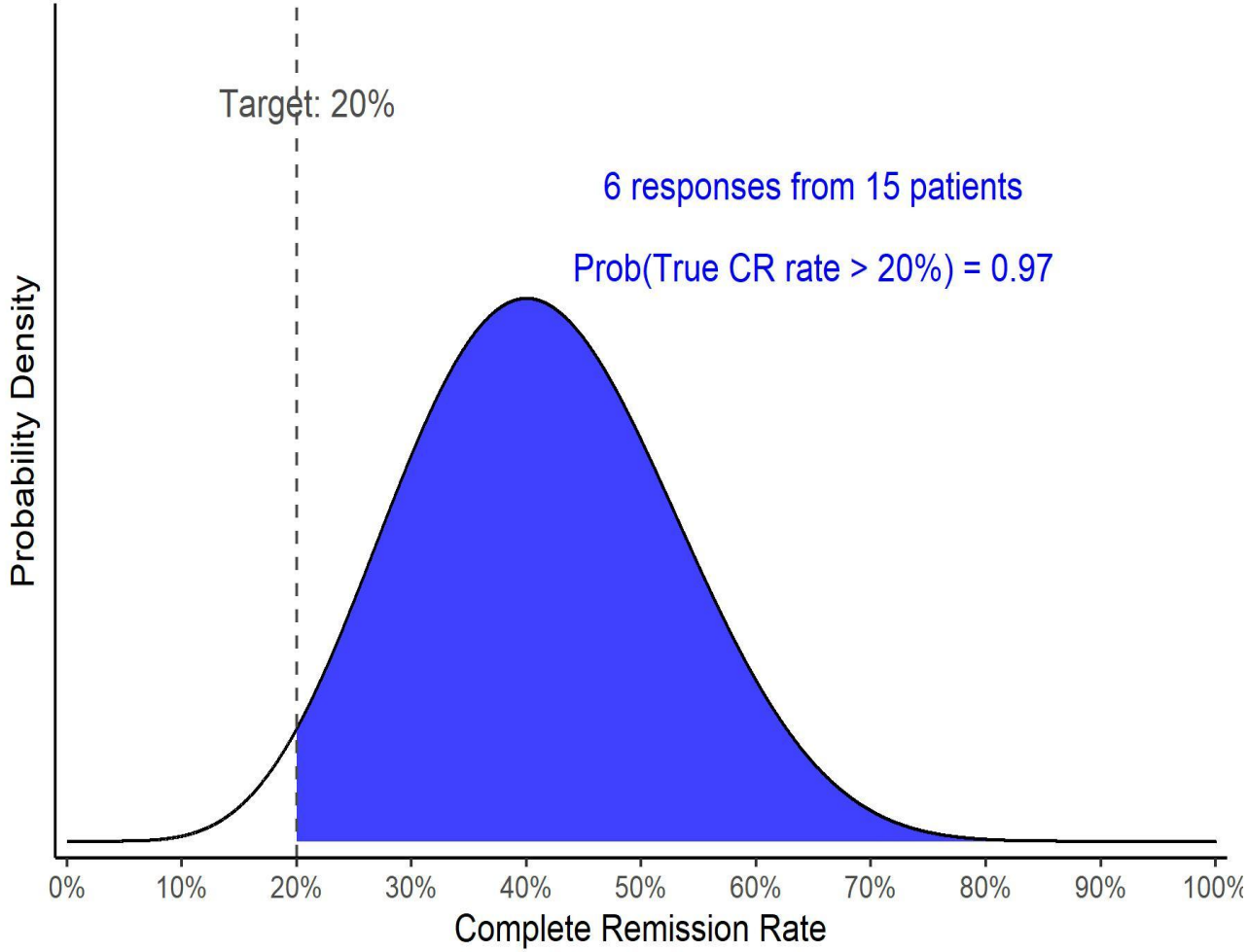
Observed CR rate = 40%

Bayesian estimate of true CR rate = 41%

95%CrI: (20%, 65%)

P(True CR rate > 20%) = 0.97

Go



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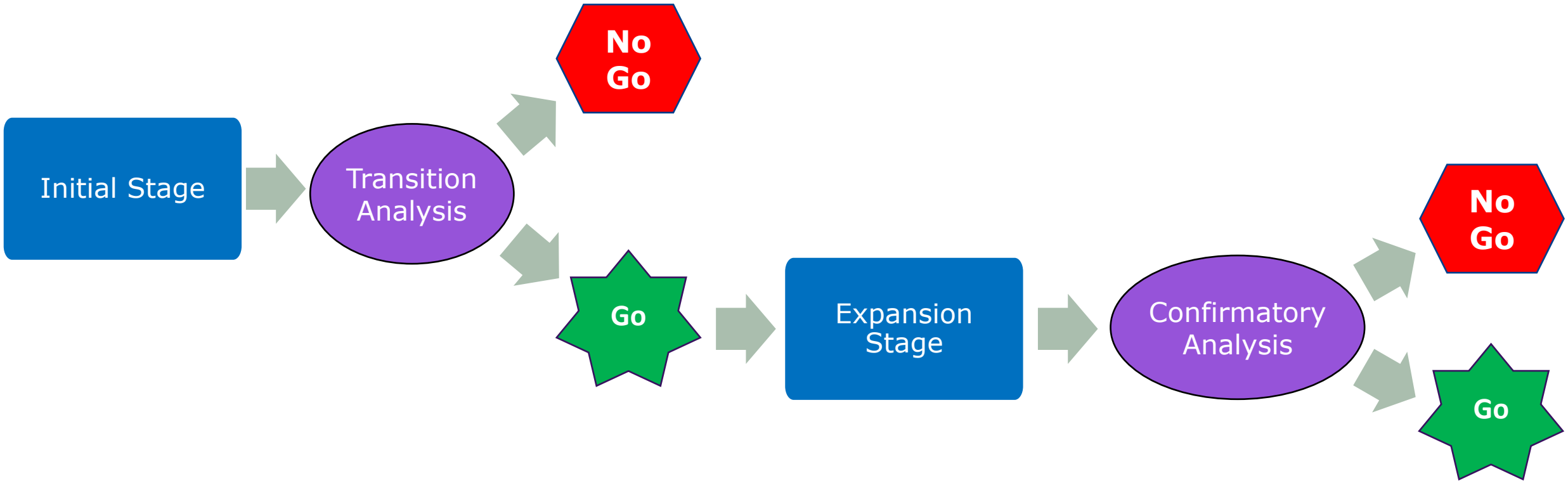
Bayesian Approach Allows Cumulative Learning

Interim Analysis Timeline



Regular interim analyses allow early stopping for futility

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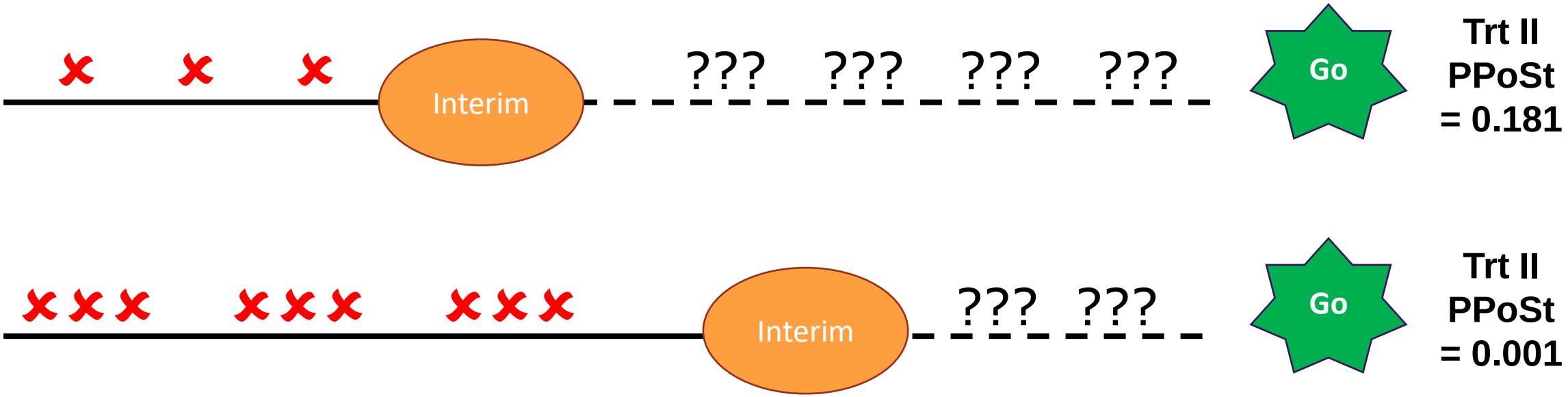
Statistical Analysis Plan for Interims

Using posterior probability distributions, calculate:

PPoS: Predicted Probability of Success

PPoSt = P(GO decision at N=15 | prior and current observed data)

PPoSc = P(GO decision at N=30 | prior and current observed data)



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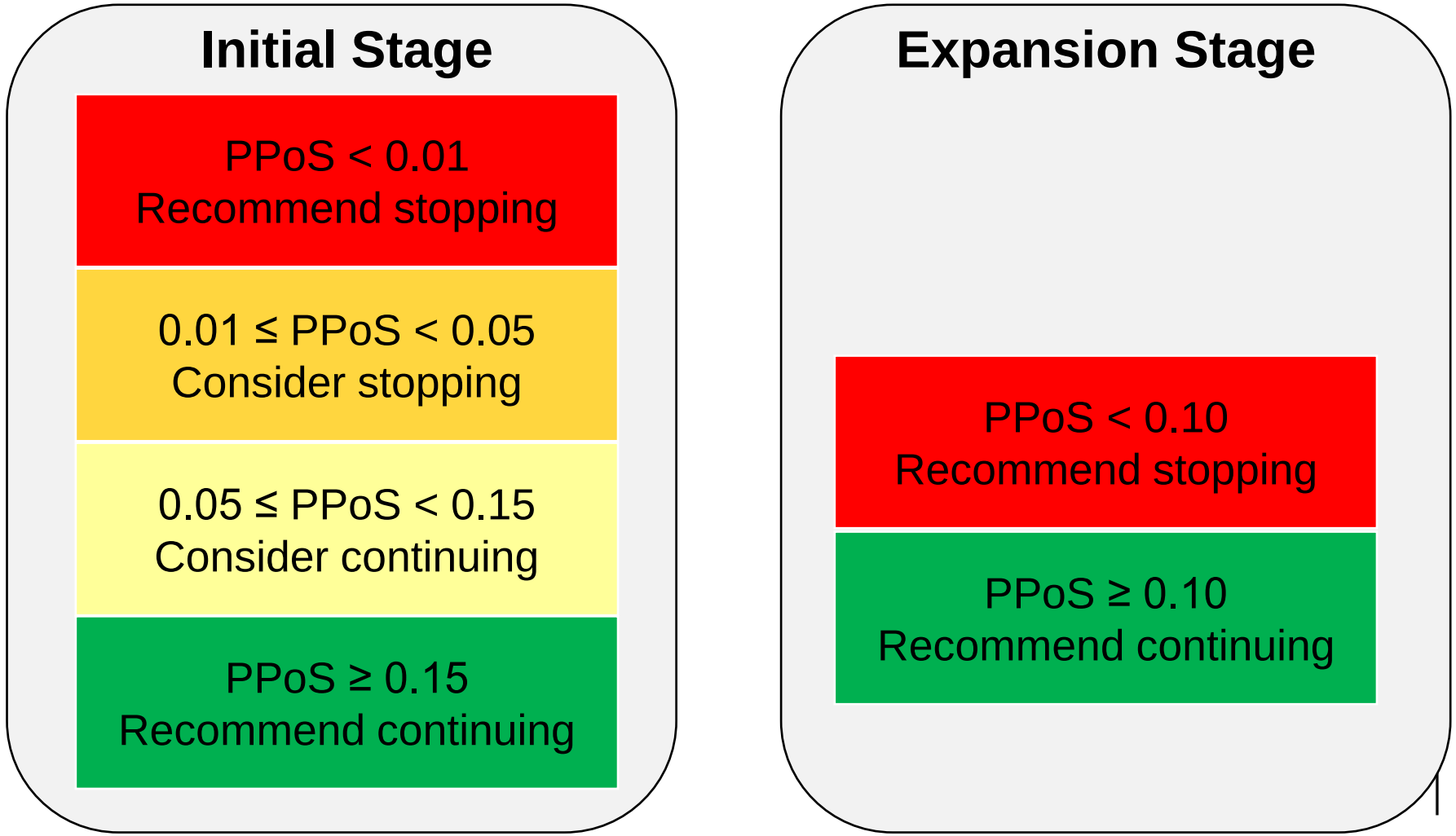
Interim Analysis Guidelines

Use Predicted Probability of Success (**PPoS**) for decision-making at interim analyses



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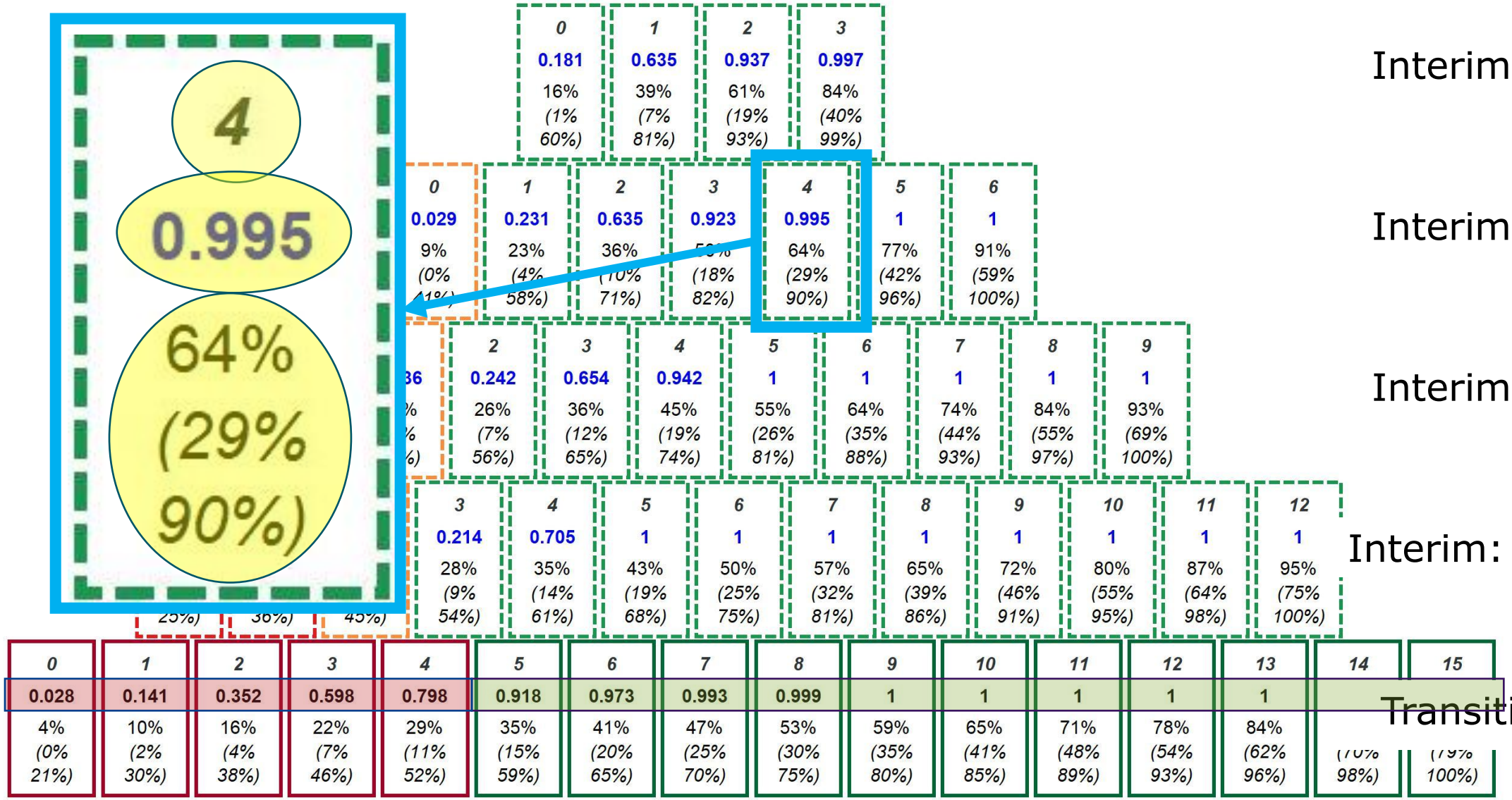
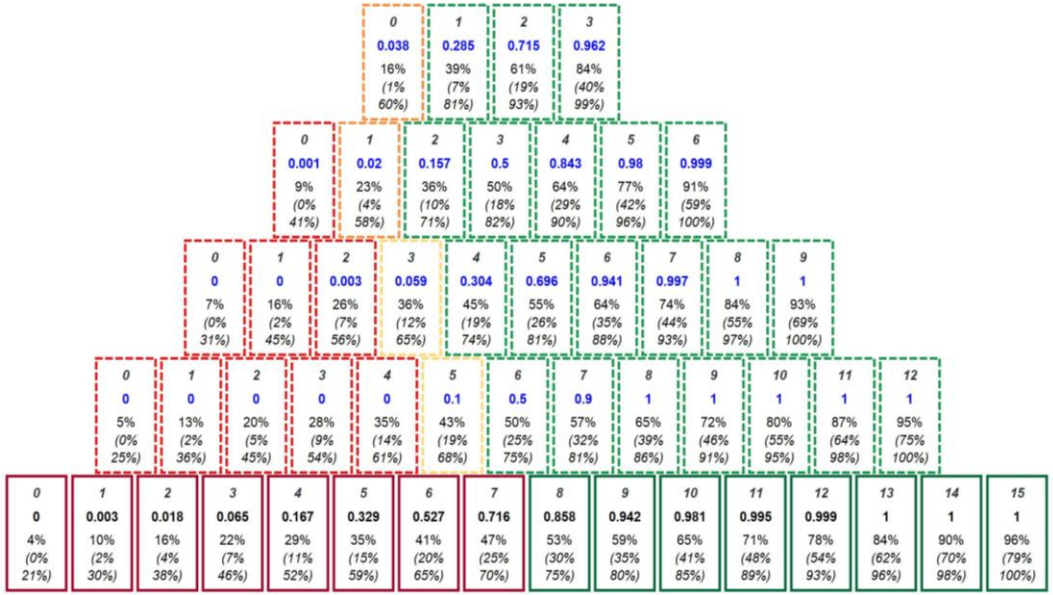
Visual Representation Using Efficacy Transition Pathways

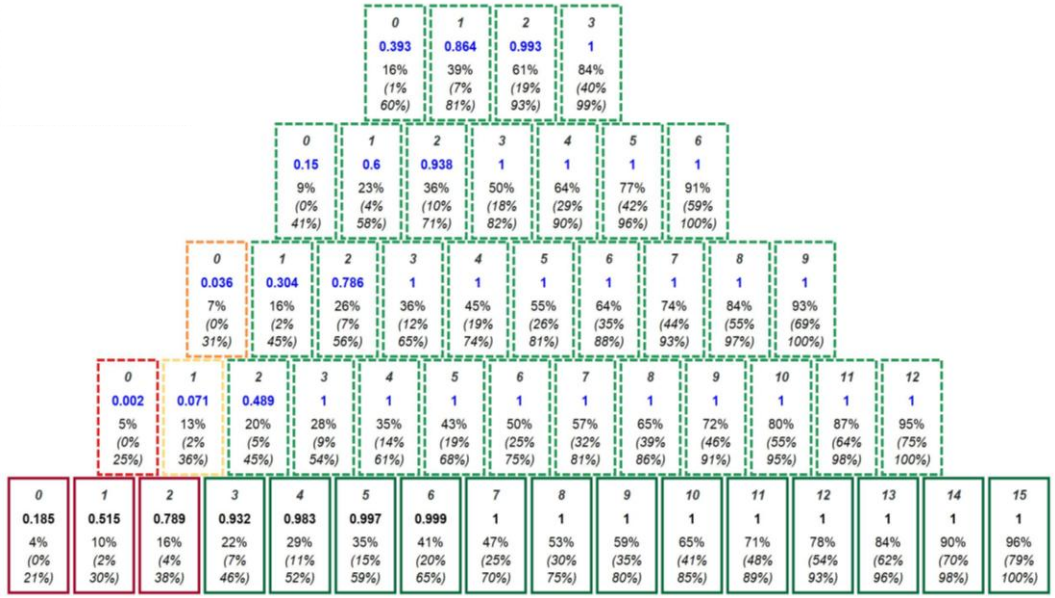


Efficacy Transition Pathways: Initial Stage for All Treatment Arms

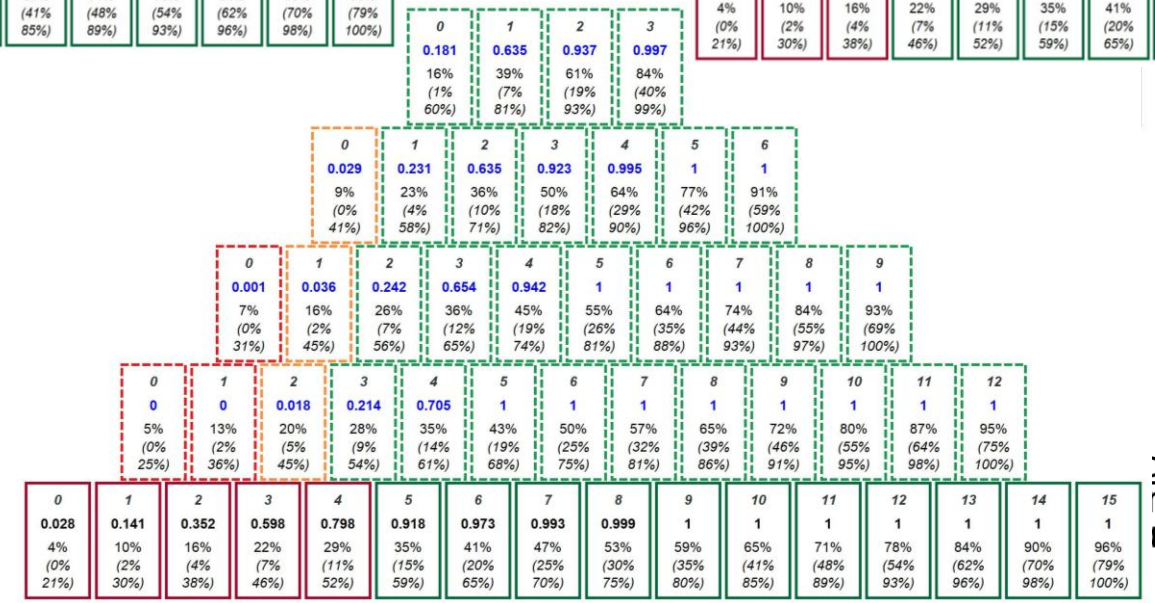
Treatment Arm Ia



Treatment Arm Ib / III



Treatment Arm II



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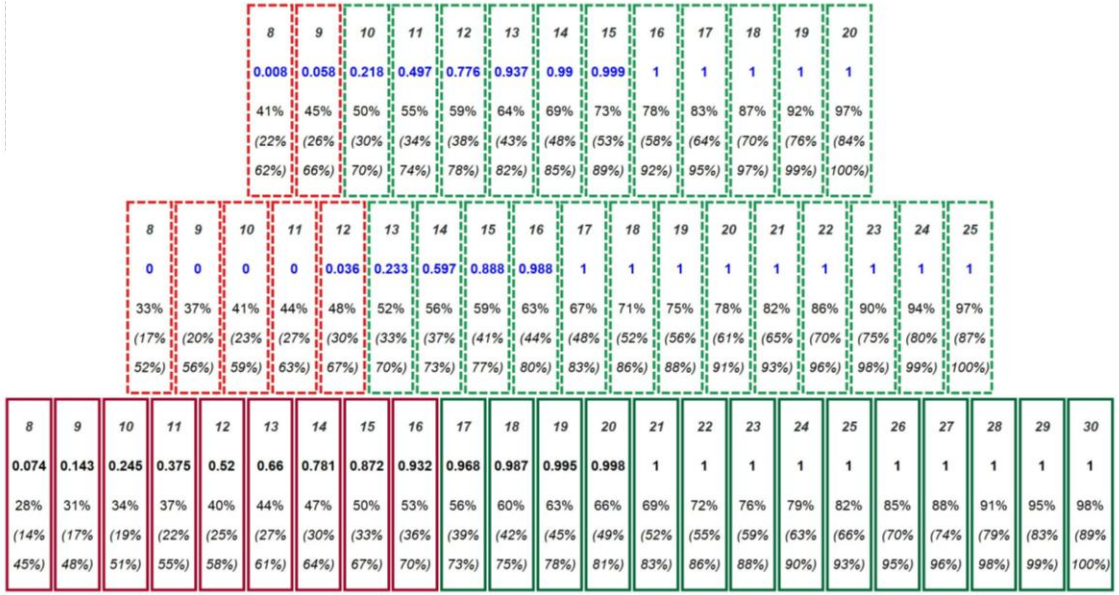
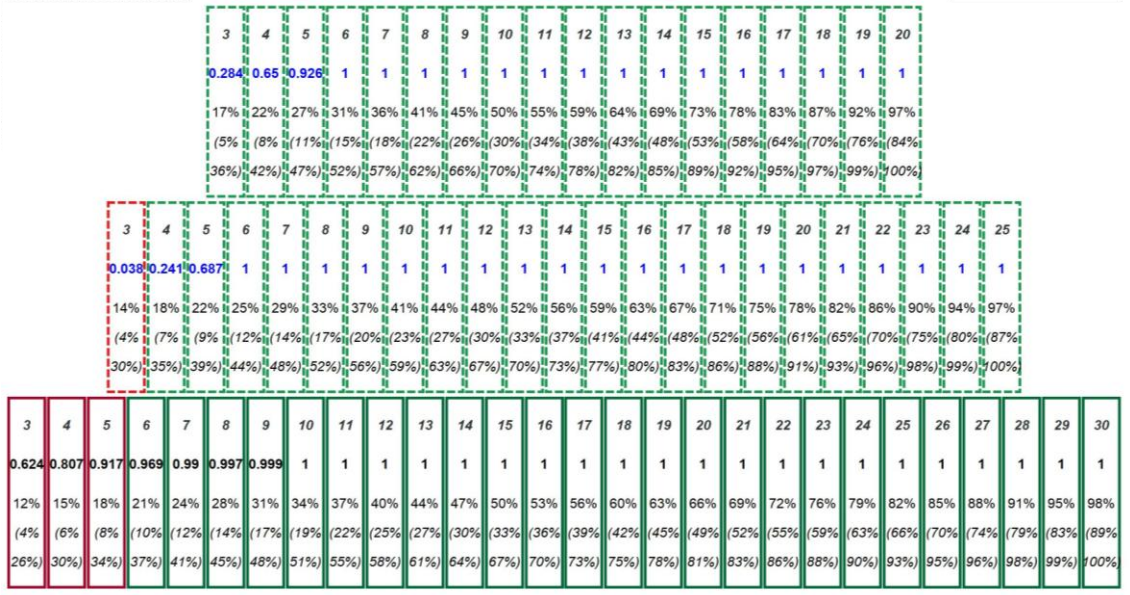
Efficacy Transition Pathways: Expansion Stage for All Treatment Arms

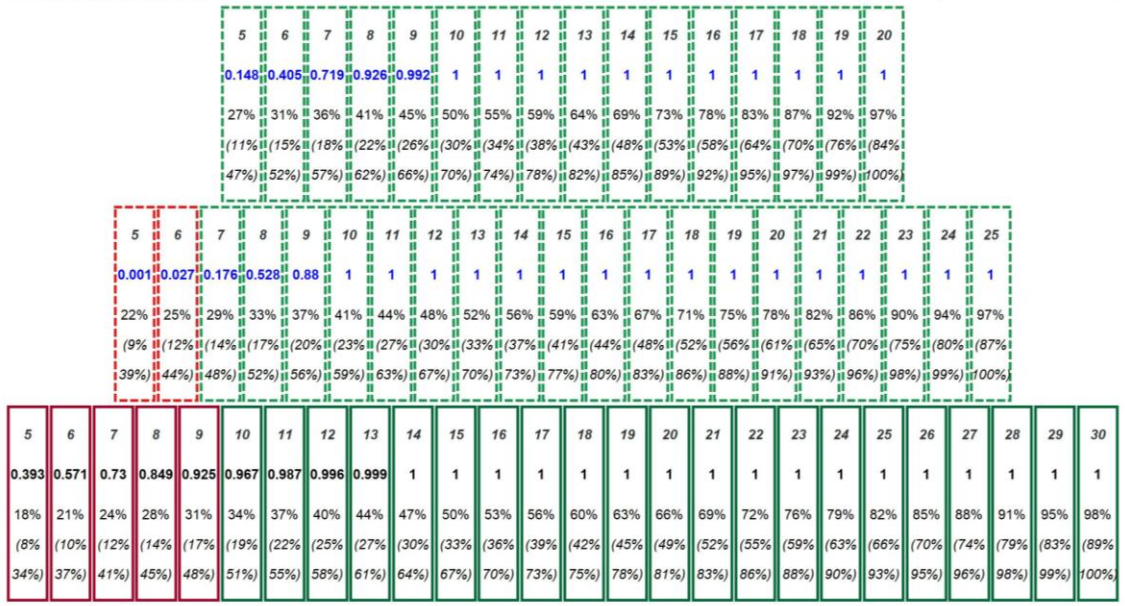
Treatment Arm Ia



Treatment Arm Ib / III



Treatment Arm II



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Operating Characteristics
Example: Treatment Arm Ia (Target Response Rate 40%)

	True Response Rate	I1 N=3	I2 N=6	I3 N=9	I4 N=12	Transition N=15	I6 N=20	I7 N=25	Confirmatory N=30		Overall T1E	Overall Power
		P(Stop)	P(Stop)	P(Stop)	P(Stop)	P(Stop)	P(Stop)	P(Stop)	P(Stop)	P(GO)		
Multi-Stage N=30	40%	0	0.046	0.189	0.215	0.338	0.044	0.061	0.068	0.039	**0.039**	
	65%	0	0.002	0.010	0.017	0.086	0.008	0.014	0.047	0.818		**0.818**
One-stage N=30	40%	-	-	-	-	-	-	-	0.952	0.048	**0.048**	
	65%	-	-	-	-	-	-	-	0.127	0.873		**0.873**

- <5% Type I error and >80% ‘power’ for absolute increase in response rate of 25%
- Target set low (with certainty set high) so this improvement is feasible
- Multiple interims has minimal impact:
  - improves Type 1 error rate but reduces power

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Bayesian design allows greater flexibility to maximise the utility of the trial in this rare paediatric cancer

- Target recruitment not met, trial will still be informative
  - E.g. In Treatment Arm Ia, if trial gives **5 ORs out of 9 patients**
  → **p(true OR rate ≥ 40%) = 0.83**
- External evidence that becomes available can be incorporated to aid decision-making
  - Supplementary analysis with informative prior
  - Important in rare cancers when any evidence is limited and valuable
- Flexibility for multiple interim analyses
  - allows trial to stop for futility as early as possible
  - minimises number of children exposed to ineffective treatments
  - allows pipeline of assets to be evaluated efficiently

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Bayesian analysis generates statistics that allow intuitive decision-making

- Bayesian final analysis
  - E.g. In Treatment Arm Ia, if trial gives **13 ORs out of 30 patients (43%)**
    → **p(true OR rate ≥ 40%) = 0.66**
  - Easily understood and interpreted by clinicians and decision-makers
  - No equivalent statistic in a non-Bayesian framework
- Bayesian interim analysis
  - Predicted probability of success allows intuitive futility decisions
  - E.g. In Treatment Arm Ia, if trial gives **4 CRs out of 9 patients**
    → **p(GO decision at n=15) = 0.30**
  - Allows us to include orange and yellow 'flags' as well as formal stopping
- Frequentist analysis
  - P-values well-known to be widely misunderstood and misinterpreted
  - Simon's two-stage design does not generate probabilities, the analysis is based only on the number of CRs required for a GO decision

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Summary and Discussion

- Trial designed to be practice-changing
- Bayesian design allows flexibility and intuitive decision-making with small numbers of patients
- Early involvement of regulators, ethics committees, investigators and patients essential to ensure any concerns on the design can be addressed
- EMA Qualification Advice process completed
- Pre-Investigational New Drug (IND) consultation process completed with US Food & Drug Administration (FDA)
- Feedback from regulators incorporated into the protocol
- Plan to revisit evidence generation discussions after the initial stage
- Supplementary analysis may include comparison to synthetic control

EUROPEAN MEDICINES AGENCY
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25 March 2022
EMADOC-1700519818-746444
Executive Director

Letter of support for the Global Platform Study of Novel Medicines in Paediatric and Adolescent Relapsed and Refractory B-cell Non-Hodgkin Lymphoma (Glo-BNHL platform)

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