

Bayesian Biostatistics Conference 2025

Using Bayesian Trial Designs to Change Clinical Practice in Rare Diseases

Lucinda Billingham

Professor of Biostatistics and Director of Biostatistics
Cancer Research UK Clinical Trials Unit
University of Birmingham

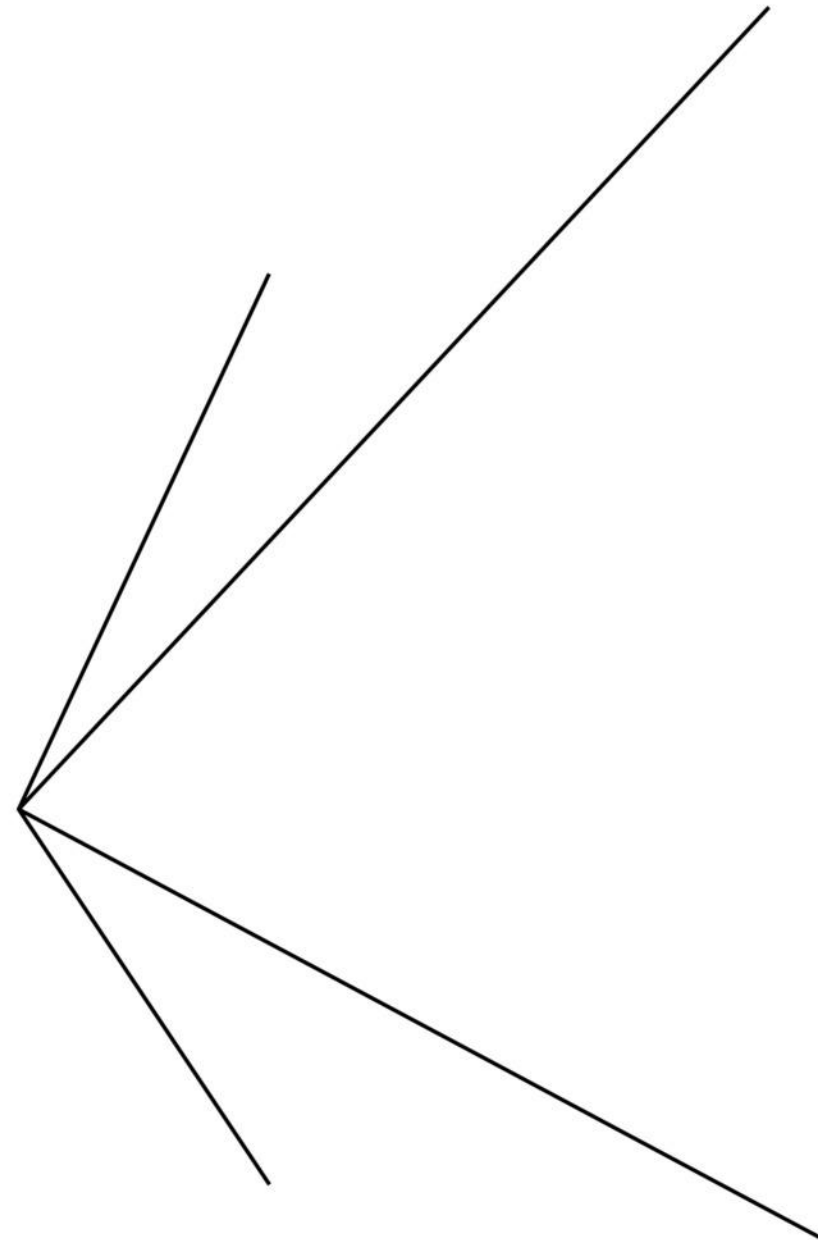


**CANCER
RESEARCH
UK**

Birmingham
Cancer Research UK
Clinical Trials Unit



**UNIVERSITY OF
BIRMINGHAM**



Illustrative Examples from the Cancer Research UK Clinical Trials Unit at University of Birmingham

- **DETERMINE Trial:** UK platform trial repurposing licensed drugs for molecular-driven rare cancers
- **Glo-BNHL Trial:** Global platform trial investigating multiple classes of drugs for ultra-rare paediatric B-cell Non-Hodgkin Lymphoma

Both designed to be practice-changing



CANCER
RESEARCH
UK

Birmingham
Cancer Research UK
Clinical Trials Unit



UNIVERSITY OF
BIRMINGHAM

The DETERMINE Trial – A Collaborative Effort

The DETERMINE team is comprised of multiple experienced clinicians and researchers that will be working closely with CRUK and its various partner organisations

Key individuals



Dr Krebs
CI/Clinical lead
 The University of Manchester



Dr Marshall
Paediatric lead
 The ROYAL MARSDEN
NHS Foundation Trust



Prof Middleton
Translational lead
 UNIVERSITY OF BIRMINGHAM



Prof Billingham
Lucy Abell
Victoria Homer
Biostatisticians
 UNIVERSITY OF BIRMINGHAM



Dr Chaturvedi
Pathologist lead
 The Christie NHS
NHS Foundation Trust



Miss Gath & Mr Burchill
Patient representatives
 voice science for patient advocates
Vision On Information, Confidence & Engagement

Key organisations



Sponsor and Commercial



Trial delivery

- Clinical trial experience
- Translational research (ctDNA, genomics)

Co-Investigators / Collaborators



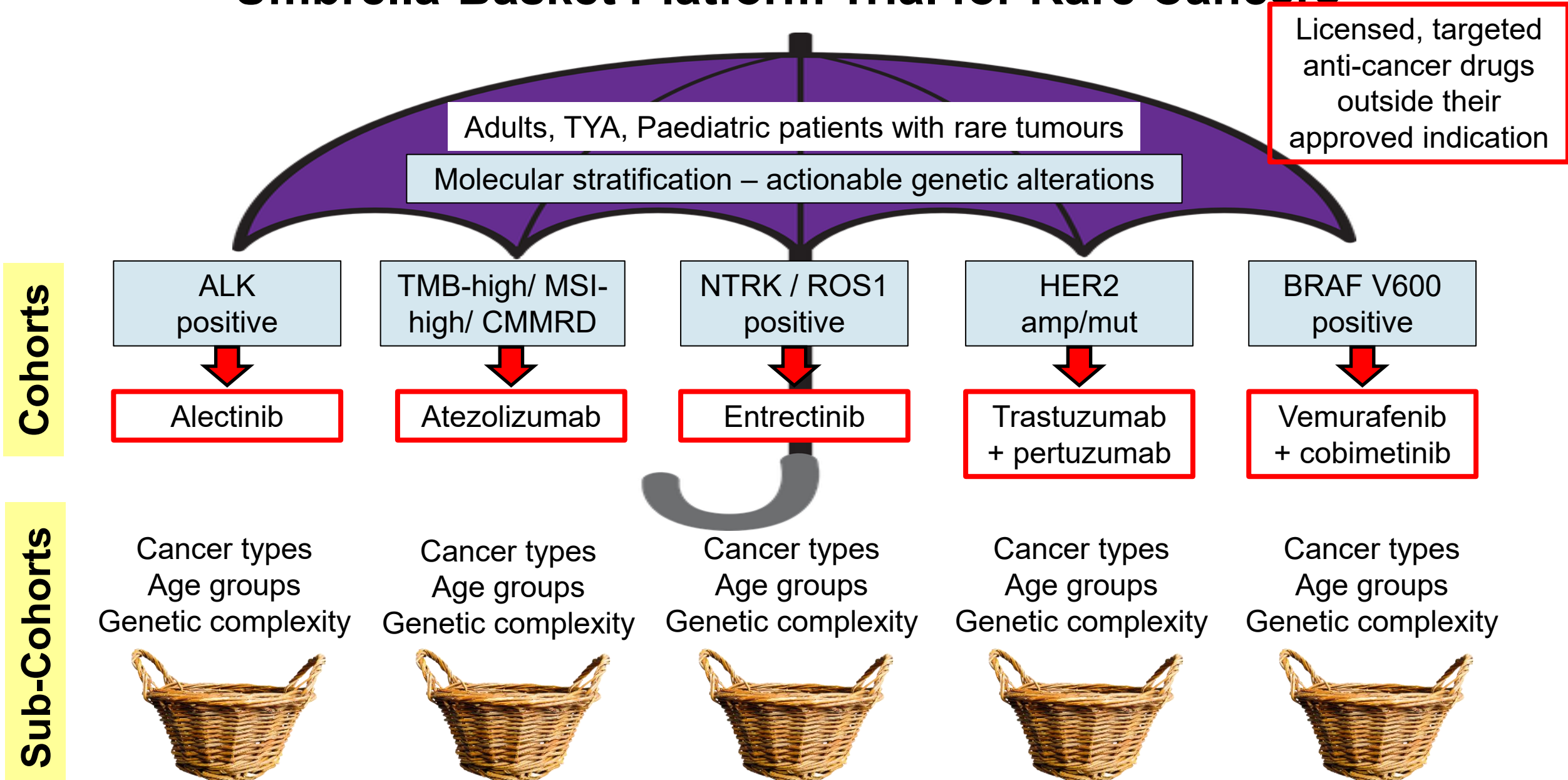
Pharma partners



Cancer Drugs Fund



DETERMINE: Potentially Practice-Changing Umbrella-Basket Platform Trial for Rare Cancers



Equivalent Trials in Europe Through the PRIME-ROSE* Consortium

DETERMINE data will be shared and aggregated with data from similar platform trials across Europe as part of its role as an **Associate Partner of the Horizons Europe-funded 'PRIME-ROSE' consortium**

24 partners
collaborating across
18 countries...



All use Simon's Two-Stage Design

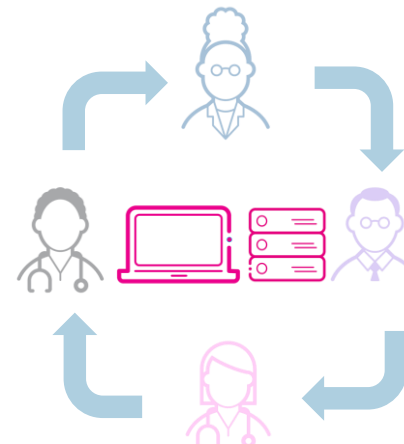


PRIME-ROSE



A key objective of the consortium is to **develop a shared data platform to:**

- ✓ Enable data sharing between trials
- ✓ Aggregate data for overlapping cohorts to support review by regulatory agencies



* PRecision Cancer MEdicine Repurposing System Using Pragmatic Clinical Trials.

Statistical Design for Trial Cohort in Each Treatment Arm of Umbrella: Single Arm Phase II

Statistics
in Medicine

Research Article

Received 5 December 2016,

Accepted 22 April 2017

Published online 7 June 2017 in Wiley Online Library

(wileyonlinelibrary.com) DOI: 10.1002/sim.7338

BOP2: Bayesian optimal design for phase II clinical trials with simple and complex endpoints

Heng Zhou,^{id} J. Jack Lee and Ying Yuan^{*†}

Department of Biostatistics, The University of Texas MD Anderson Cancer Center, Houston, Texas 77030, U.S.A.

^{*}Correspondence to: Ying Yuan, Department of Biostatistics, The University of Texas MD Anderson Cancer Center Houston, TX 77030, U.S.A.

[†]E-mail: yyuan@mdanderson.org

- Single arm phase II comparable to Simon's two-stage design
- **Binary outcome measure:** response / no response
- Based on a Dirichlet-multinomial model → standard **beta-binomial conjugate model** for a single binary outcome
- At each interim, GO/NoGO decision based on **posterior probabilities**
- BOP2 design explicitly **controls the type I error rate** and **optimises power** under the alternative hypothesis for a given sample size

Specifying the Parameters of the BOP2 Design for DETERMINE

The screenshot shows a web browser window displaying the BOP2 design specification page. The browser address bar shows the URL: trialdesign.org/one-page-shell.html#BOP2. The page title is "BOP2: Bayesian Optimal Phase II Design with Simple and Complex Endpoints". The page includes a navigation menu with "HOME", "SOFTWARE", "OUR TEAM", "PUBLICATIONS", and "CONTACT". The authors listed are Heng Zhou, Yujie Zhao, Ying-Wei Kuo, Nan Chen, Yanhong Zhou, J. Jack Lee and Ying Yuan, from the Department of Biostatistics, The University of Texas MD Anderson Cancer Center.

The main content area is divided into several sections, each with a question mark icon for help:

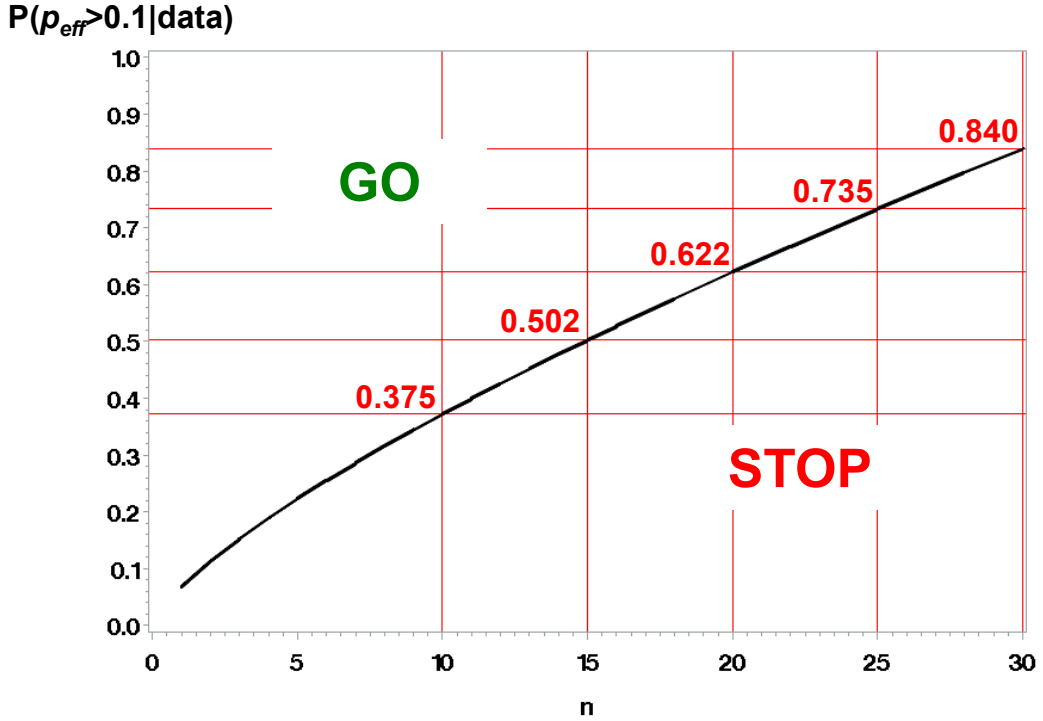
- Endpoints:** Radio buttons for Binary Efficacy (selected), Binary Toxicity, Efficacy & Toxicity, Multiple Efficacy, Ordinal Efficacy, and Time To Event.
- Interims:** A text input field containing "10 15 20 25 30".
- Null Hypothesis:** A text input field for Response Rate containing "0.1".
- Alternative Hypothesis:** A text input field for Response Rate containing "0.3".
- Type I Error Rate (One-sided):** A text input field containing "0.1".
- Prior Specification:** A checkbox for "Use default vague prior with prior effective sample size = 1 (Recommended)" which is checked. Below it is a button labeled "Calculate Stopping Boundaries".

Annotations on the right side of the image provide context for the values entered:

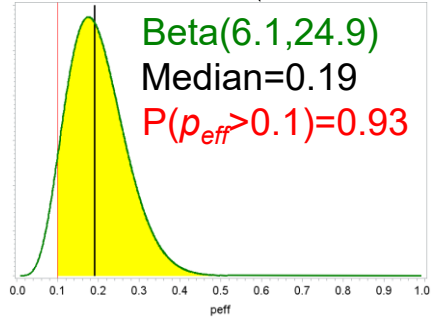
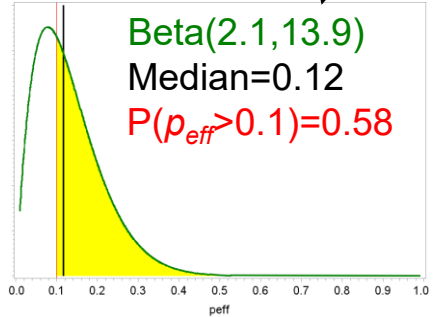
- Binary efficacy:** p_{eff} denotes true response rate
- Sample sizes when interim analyses are to be performed (n), ending with total sample size (N):** 10 15 20 25 30
- Null hypothesis:** $p_{eff} \leq 0.1$
Level below which treatment is unacceptable
- Alternative hypothesis:** $p_{eff} = 0.3$
Level at which we want trial to have a high chance of correctly claiming that the treatment is acceptable (i.e. power)
- Type I error rate (one-sided):** 0.1
- Use default vague prior with effective sample size of 1 i.e. Beta(0.1, 0.9)**

The Windows taskbar at the bottom shows the time as 21:30 on 02/10/2022.

Decision-Making at Interim and Final Analyses for Trial Cohorts in DETERMINE



	n=10	n=15	n=20	n=25	N=30
STOP	0	≤1	≤2	≤3	≤5
GO	1+	2+	3+	4+	6+



p_{eff} : True response rate

Beta-Binomial conjugate analysis will generate a posterior probability distribution for p_{eff}

Prior: $p_{eff} \sim \text{Beta}(a_0, b_0) = \text{Beta}(0.1, 0.9)$

Data: r responses out of n patients

Posterior: $p_{eff} | r, n \sim \text{Beta}(a_0 + r, b_0 + n - r)$

BOP2 decision rule:

$$Pr(p_{eff} > 0.1 | data) < \lambda \left(\frac{n}{N} \right)^\alpha$$

n=interim sample size
N=final sample size

where $\lambda=0.84$ and $\alpha=0.74$ are design parameters optimized to maximize power

This decision rule leads to the stopping boundaries that yields a statistical power of **0.891** under H_1

Challenges of the Basket Design Element of the Trial

Cancer types
Age groups
Genetic complexity



Sub-Cohorts

- Aim of trial: to evaluate treatments in a diversity of rare cancers
- In each treatment arm, the number and type of sub-cohorts to be recruited is difficult to predict
- Need to ensure that no single type of cancer is over-represented on a treatment arm
 - **Lack of efficacy** in a single type of cancer – could stop treatment arm early and deny other types of rare cancers the opportunity for evaluation
 - **Good efficacy** in a single type of cancer – will not allow evaluation across other rare cancers
- As a sub-cohort emerges it is separated from the main trial cohort and evaluated separately, allowing the main trial cohort to continue recruitment to N=30
- Flexible adaptive Bayesian design has allowed the design to be adapted to accommodate this issue

Adapting the Bayesian Design for Sub-Cohort Analysis (Why 7 is the 'magic number'!)

Sub-Cohort decisions:

Predicted Probability of Success (PPoS) = p (GO decision at $N=30$ | current data, prior)

Decision Rule for Sub-Cohorts at Interims:

if $PPoS < 0.10$ then STOP i.e. introduce sub-cohort **exclusion** criteria

Subcohort size n	Number of DCB for STOP decision	PPoS	P(correct STOP) i.e. when TRUE DCB rate = 10%	P(incorrect STOP) i.e. when TRUE DCB rate = 30%
7	0	0.008	0.48	0.08
10	0	0.003	0.34	<0.05
15	1	0.025	0.56	<0.05
20	2	0.035	0.67	<0.05

Need these probabilities to be **small** i.e. <0.10

- Umbrella design:
 - Allows multiple licensed targeted treatments to be tested in different molecular-driven cancers
 - BOP2 provides simple Bayesian alternative to Simon's two stage design
- Basket design:
 - Number and type of sub-cohorts to be recruited onto each treatment arm difficult to predict
 - Extra challenges around 'swamping' arose as recruitment was underway
 - Adaptive Bayesian design allows extra decision-making to be included
 - Some simple operating characteristics generated but simulations of whole trial design difficult when the number and type of sub-cohorts difficult to predict
- Extra complexities:
 - Co-primary binary outcomes
 - Funds for potential decisions need to be negotiated

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



CANCER
RESEARCH
UK

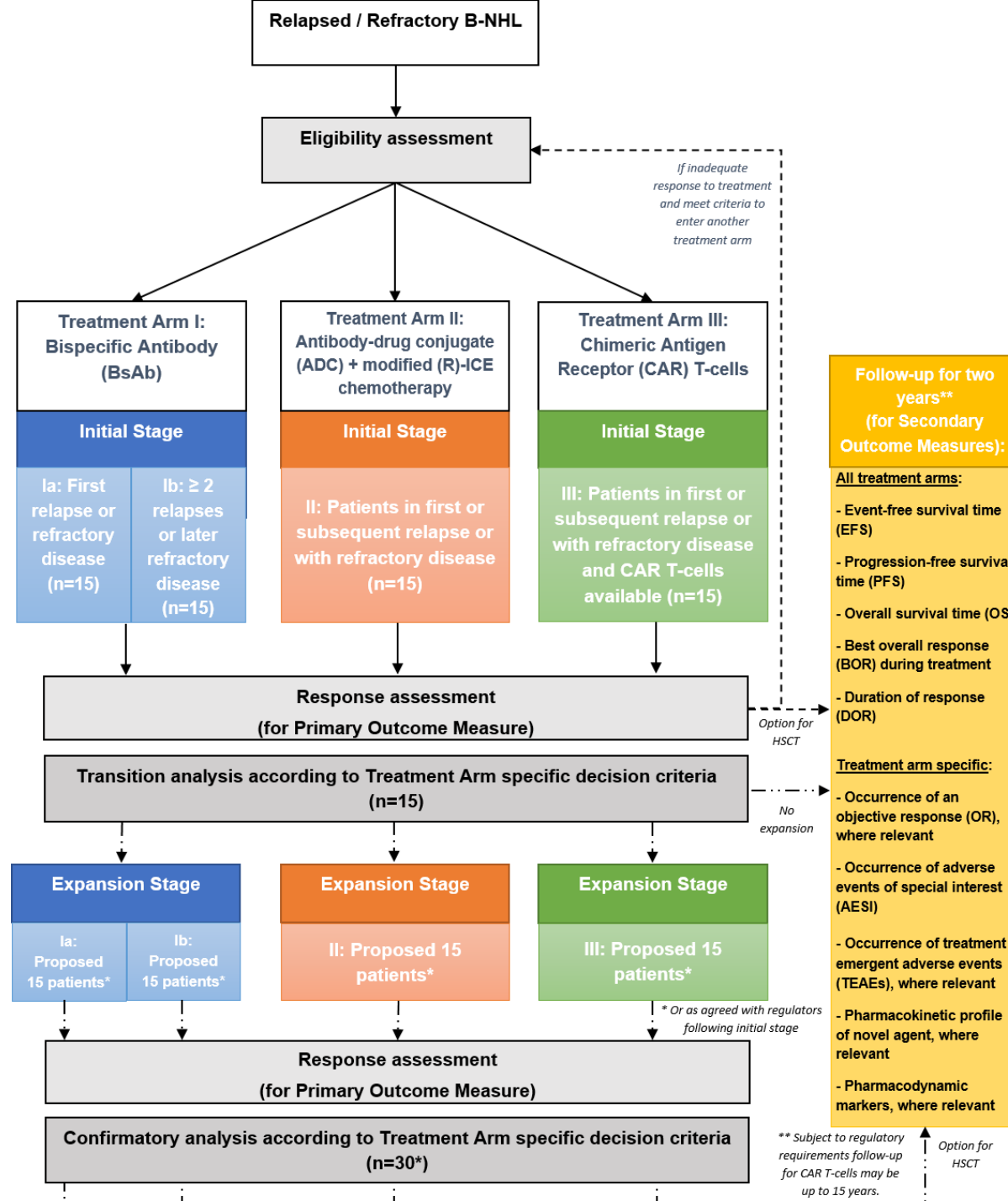
Birmingham
Cancer Research UK
Clinical Trials Unit



UNIVERSITY OF
BIRMINGHAM

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

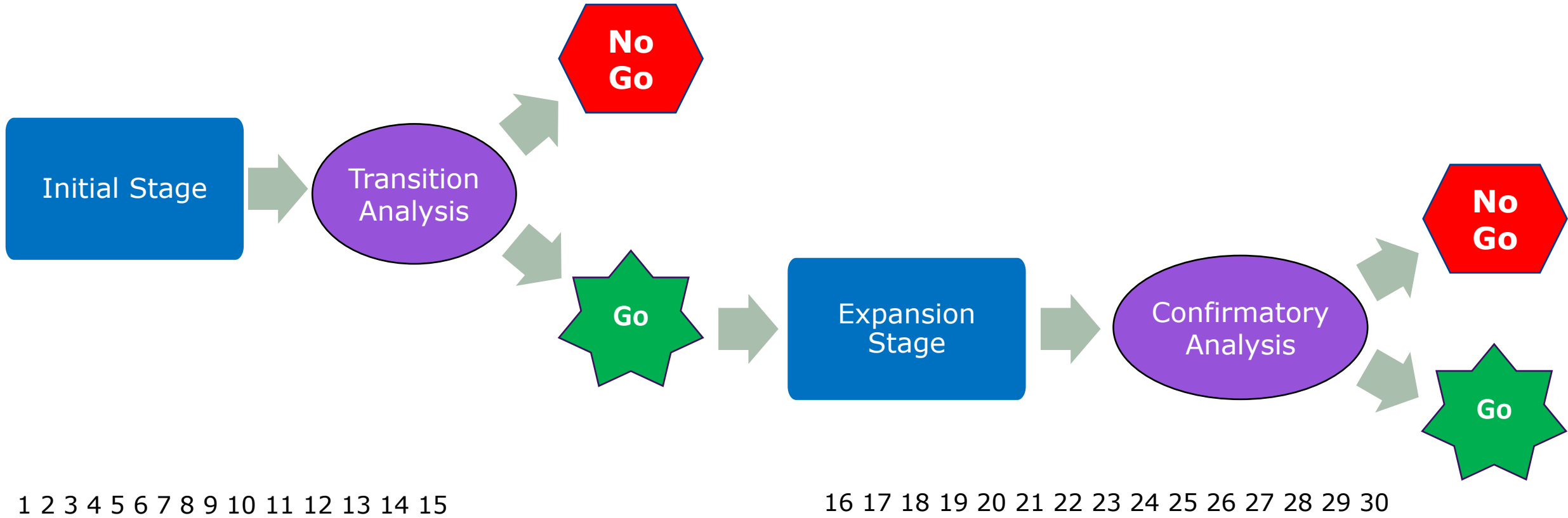


Trial Design: Treatment Arm Specific Criteria

	Treatment Arm Ia	Treatment Arm Ib	Treatment Arm II	Treatment Arm III
Population	1 st Relapse / refractory B-NHL	B-NHL in >1 st relapse	B-NHL in 1 st 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%



Decision Analysis Timeline



Patients Recruited



CANCER
RESEARCH
UK

Birmingham
Cancer Research UK
Clinical Trials Unit



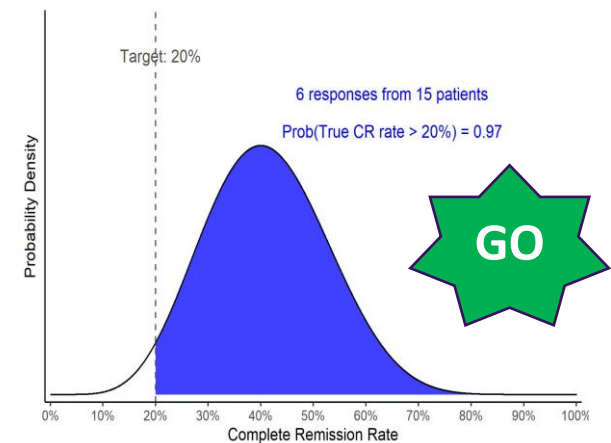
UNIVERSITY OF
BIRMINGHAM

Statistical Analysis Plan

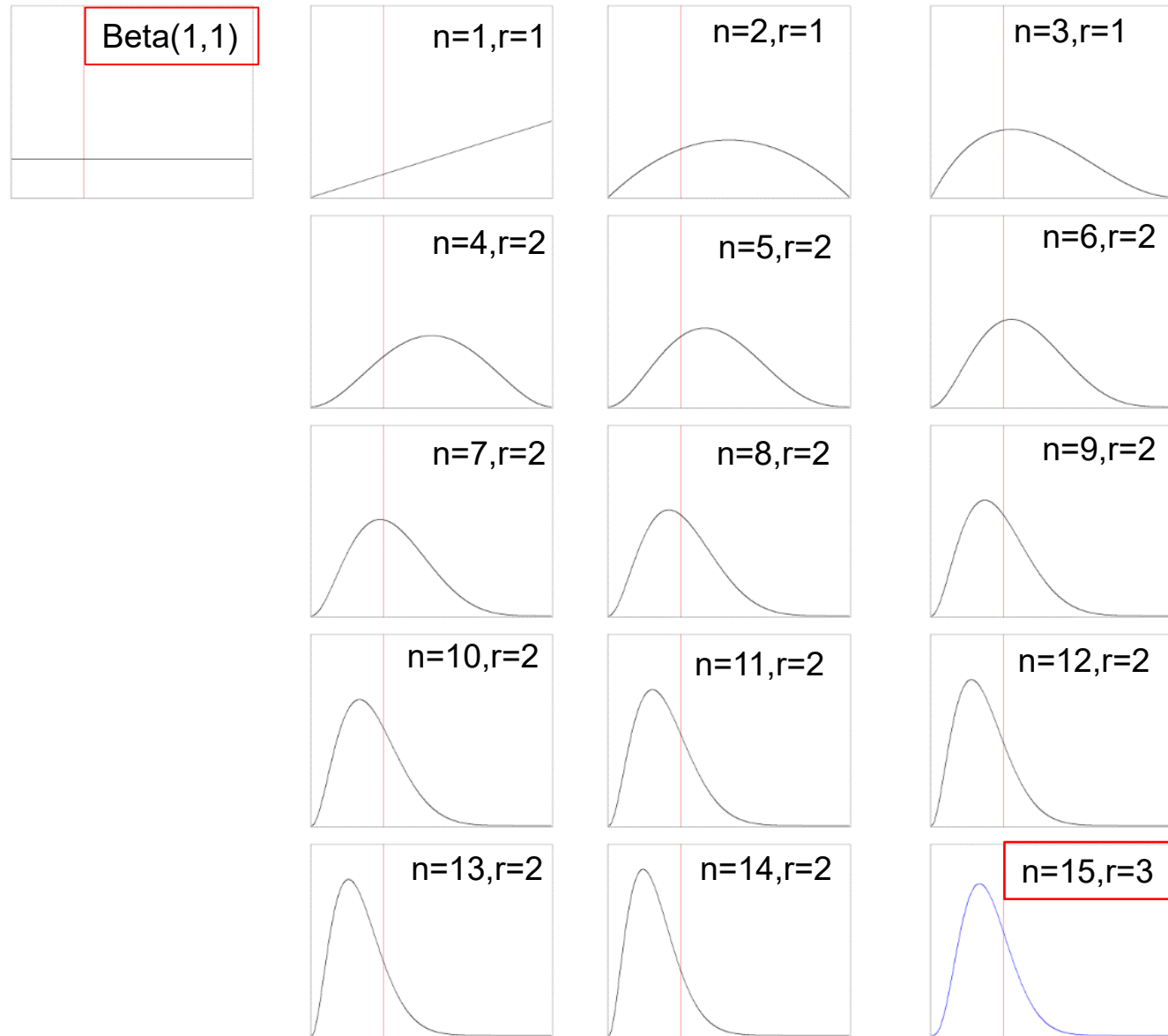
- **Bayesian beta-binomial conjugate analysis**
 - Binomial likelihood: r responses / n patients
 - Beta prior distribution: $\text{beta}(a,b)$
 - Minimally informative: $\text{beta}(1,1)$
 - Beta posterior distribution: **$\text{beta}(a+r, b+n-r)$**
- Estimation from posterior probability distribution: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

Treatment Arm II Transition Analysis

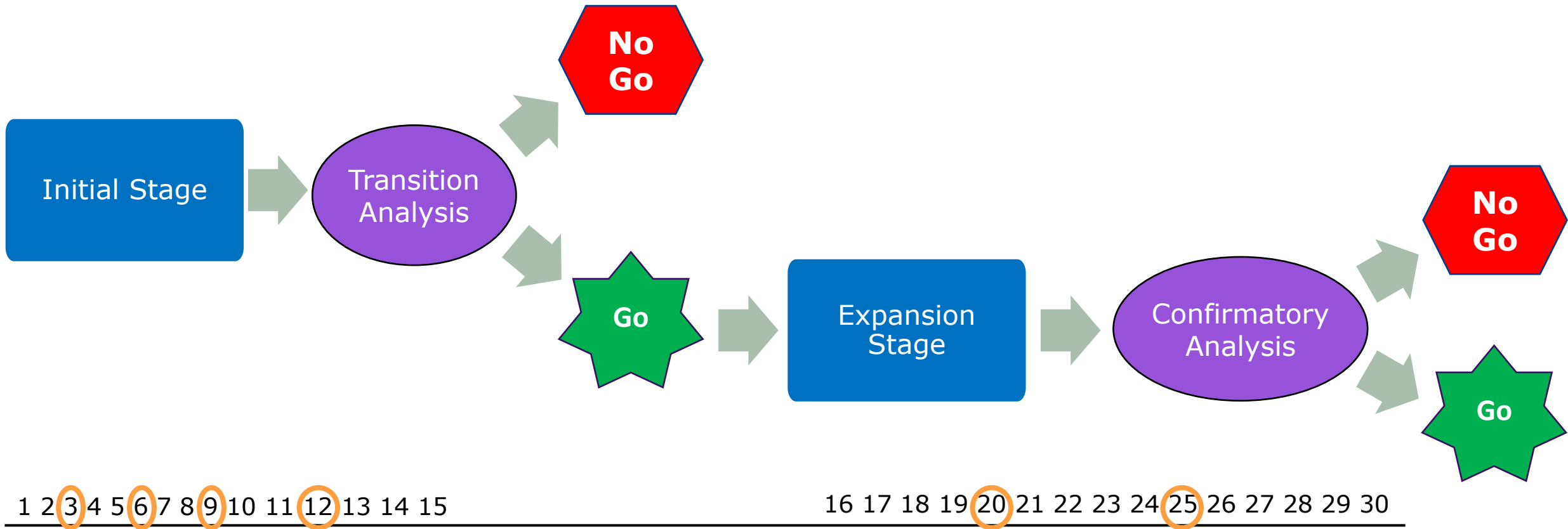
If $p(\text{True CR rate} > 20\%) > 0.80$
then GO



Bayesian Approach Allows Cumulative Learning



Interim Analysis Timeline



1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

Patients Recruited

Regular interim analyses
allow early stopping for futility



CANCER
RESEARCH
UK

Birmingham
Cancer Research UK
Clinical Trials Unit



UNIVERSITY OF
BIRMINGHAM

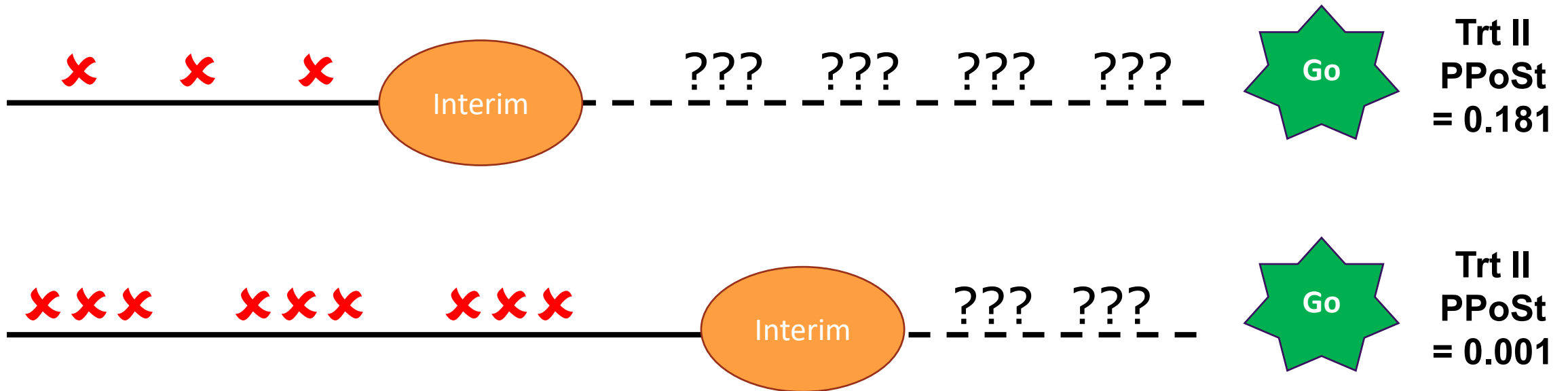
Statistical Analysis Plan for Interims

Using posterior probability distributions, calculate:

PPoS: Predicted Probability of Success

PPoS₁₅ = P(GO decision at N=15 | prior and current observed data)

PPoS₃₀ = P(GO decision at N=30 | prior and current observed data)



CANCER
RESEARCH
UK

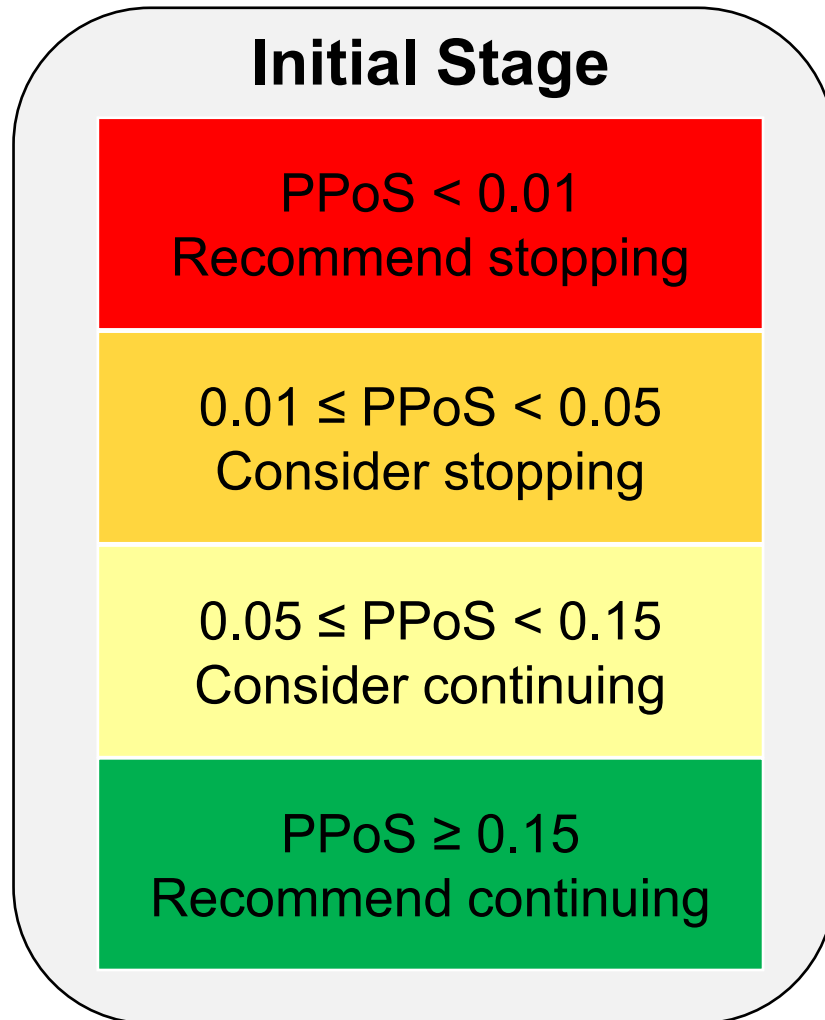
Birmingham
Cancer Research UK
Clinical Trials Unit



UNIVERSITY OF
BIRMINGHAM

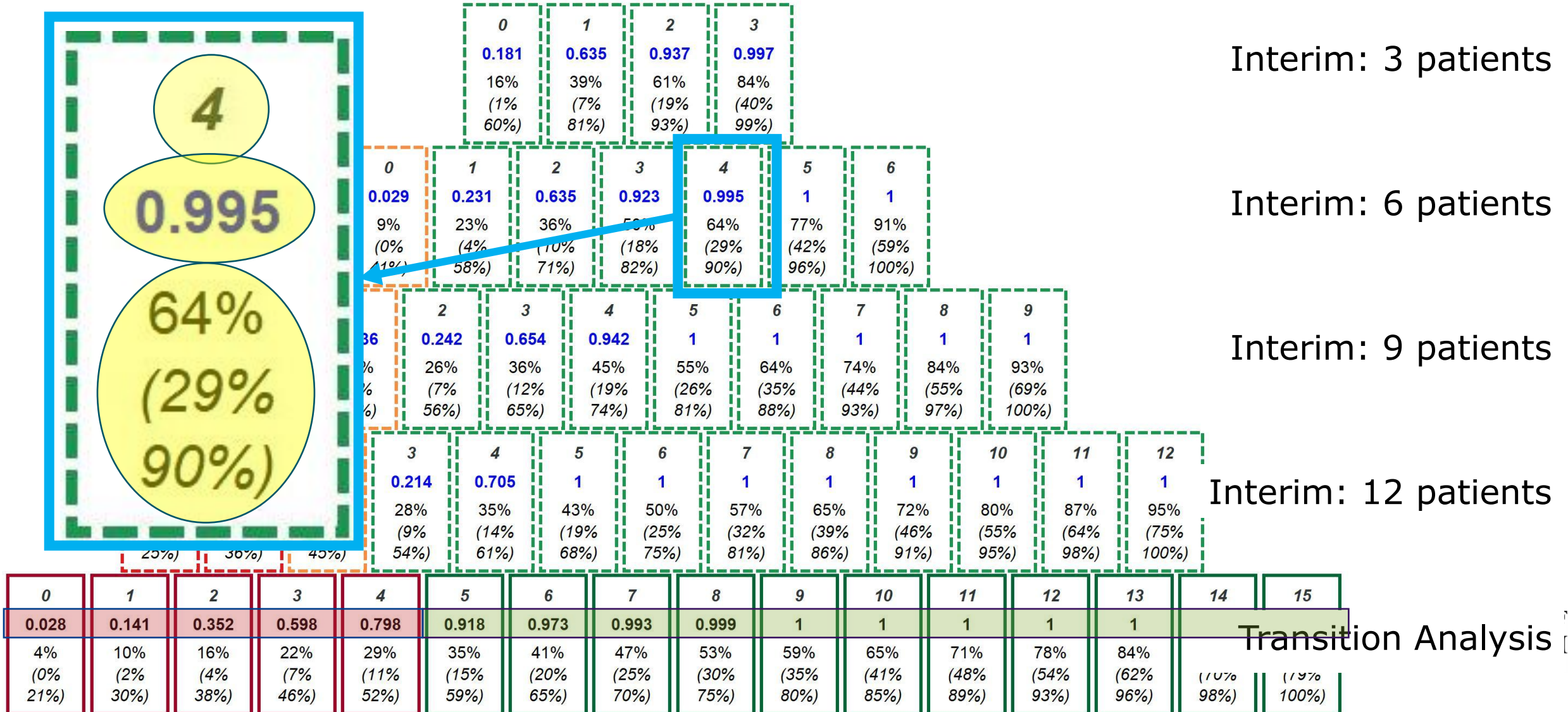
Interim Analysis Guidelines

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



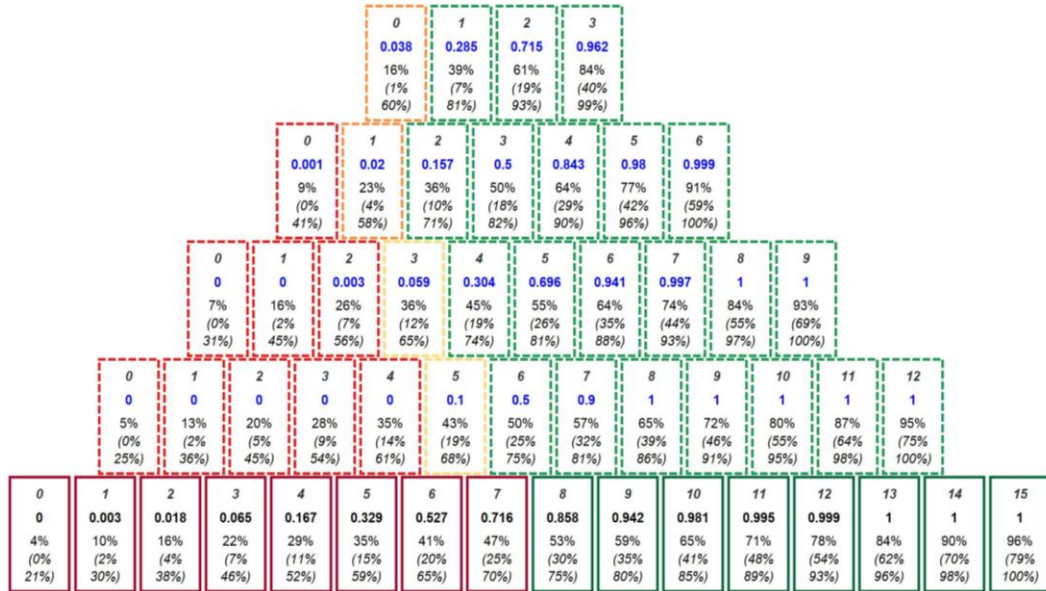
Visual Representation Using Efficacy Transition Pathways

Example: Treatment Arm II

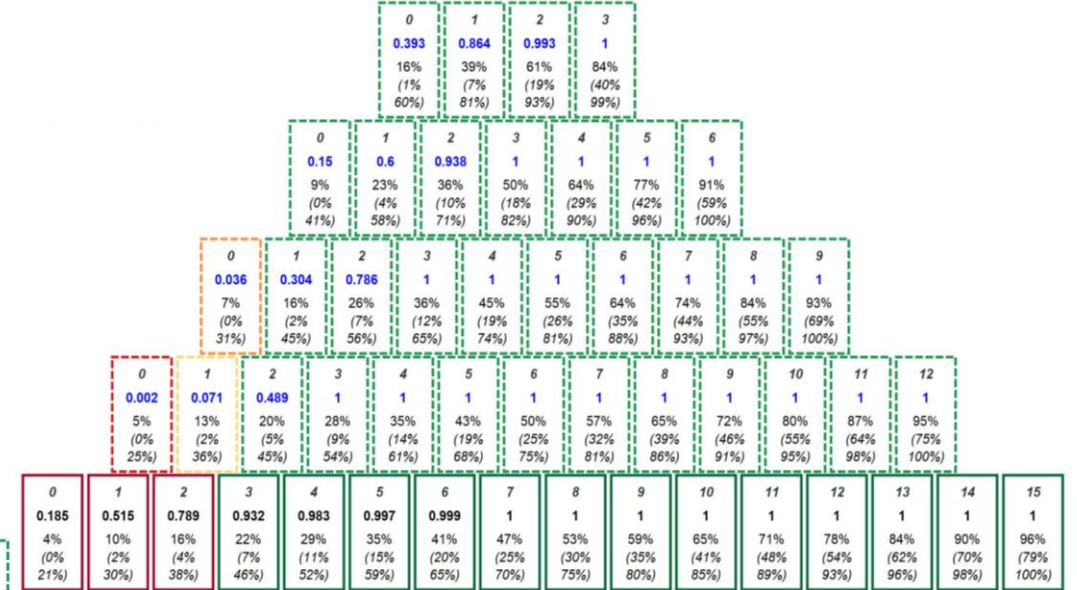


Efficacy Transition Pathways: Initial Stage for All Treatment Arms

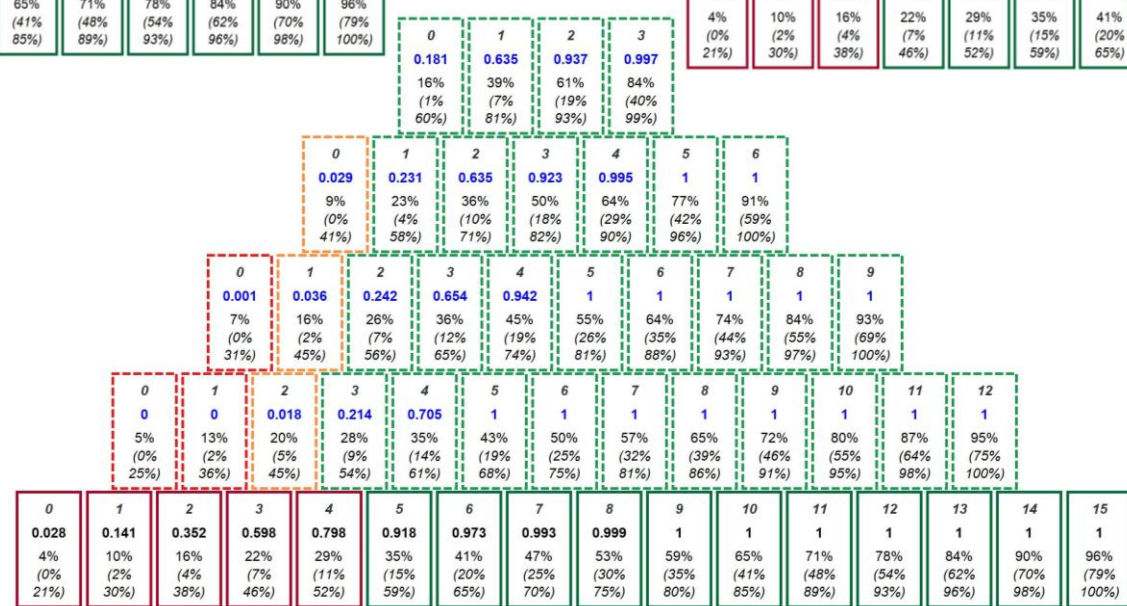
Treatment Arm Ia



Treatment Arm Ib / III



Treatment Arm II



gham
Research UK
Clinical Trials Unit



UNIVERSITY OF BIRMINGHAM

Efficacy Transition Pathways: Expansion Stage for All Treatment Arms

Treatment Arm Ia

8	9	10	11	12	13	14	15	16	17	18	19	20
0.008	0.058	0.218	0.497	0.776	0.937	0.99	0.999	1	1	1	1	1
41%	45%	50%	55%	59%	64%	69%	73%	78%	83%	87%	92%	97%
(22%)	(26%)	(30%)	(34%)	(38%)	(43%)	(48%)	(53%)	(58%)	(64%)	(70%)	(76%)	(84%)
62%	66%	70%	74%	78%	82%	85%	89%	92%	95%	97%	99%	100%

8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
0	0	0	0	0.036	0.233	0.597	0.888	0.988	1	1	1	1	1	1	1	1	1
33%	37%	41%	44%	48%	52%	56%	59%	63%	67%	71%	75%	78%	82%	86%	90%	94%	97%
(17%)	(20%)	(23%)	(27%)	(30%)	(33%)	(37%)	(41%)	(44%)	(48%)	(52%)	(56%)	(61%)	(65%)	(70%)	(75%)	(80%)	(87%)
52%	56%	59%	63%	67%	70%	73%	77%	80%	83%	86%	88%	91%	93%	96%	98%	99%	100%

Treatment Arm Ib / III

3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
0.284	0.65	0.926	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
17%	22%	27%	31%	36%	41%	45%	50%	55%	59%	64%	69%	73%	78%	83%	87%	92%	97%
(5%)	(8%)	(11%)	(15%)	(18%)	(22%)	(26%)	(30%)	(34%)	(38%)	(43%)	(48%)	(53%)	(58%)	(64%)	(70%)	(76%)	(84%)
36%	42%	47%	52%	57%	62%	66%	70%	74%	78%	82%	85%	89%	92%	95%	97%	99%	100%

3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
0.038	0.241	0.687	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
14%	18%	22%	25%	29%	33%	37%	41%	44%	48%	52%	56%	59%	63%	67%	71%	75%	78%	82%	86%	90%	94%	97%
(4%)	(7%)	(9%)	(12%)	(14%)	(17%)	(20%)	(23%)	(27%)	(30%)	(33%)	(37%)	(41%)	(44%)	(48%)	(52%)	(56%)	(61%)	(65%)	(70%)	(75%)	(80%)	(87%)
30%	35%	39%	44%	48%	52%	56%	59%	63%	67%	70%	73%	77%	80%	83%	86%	88%	91%	93%	96%	98%	99%	100%

Created using

<https://amit-patel.shinyapps.io/beta-binomialapp/>

as part of PhD thesis by Amit Patel at University of Birmingham
(paper to be published shortly)

5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
0.001	0.027	0.176	0.528	0.88	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
22%	25%	29%	33%	37%	41%	44%	48%	52%	56%	59%	63%	67%	71%	75%	78%	82%	86%	90%	94%	97%
(9%)	(12%)	(14%)	(17%)	(20%)	(23%)	(27%)	(30%)	(33%)	(37%)	(41%)	(44%)	(48%)	(52%)	(56%)	(61%)	(65%)	(70%)	(75%)	(80%)	(87%)
39%	44%	48%	52%	56%	59%	63%	67%	70%	73%	77%	80%	83%	86%	88%	91%	93%	96%	98%	99%	100%

5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
0.393	0.571	0.73	0.849	0.925	0.967	0.987	0.996	0.999	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	
18%	21%	24%	28%	31%	34%	37%	40%	44%	47%	50%	53%	56%	60%	63%	66%	69%	72%	76%	79%	82%	85%	88%	91%	95%	98%
(8%)	(10%)	(12%)	(14%)	(17%)	(19%)	(22%)	(25%)	(27%)	(30%)	(33%)	(36%)	(39%)	(42%)	(45%)	(49%)	(52%)	(55%)	(59%)	(63%)	(66%)	(70%)	(74%)	(79%)	(83%)	(89%)
34%	37%	41%	45%	48%	51%	55%	58%	61%	64%	67%	70%	73%	75%	78%	81%	83%	86%	88%	90%	93%	95%	96%	98%	99%	100%



ham
Research UK
. Trials Unit



UNIVERSITY OF
BIRMINGHAM

Operating Characteristics

Example: Treatment Arm II (Target Response Rate 20%)

	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	20%	0	0	0.134	0.155	0.547	0	0.043	0.077	0.044	0.044	
	43%	0	0	0.006	0.008	0.140	0	0.006	0.035	0.805		0.805
One-stage N=30	20%	-	-	-	-	-	-	-	0.939	0.061	0.061	
	43%	-	-	-	-	-	-	-	0.103	0.897		0.897

- <5% Type I error and >80% 'power' for absolute increase in response rate of 23%
- 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

RESEARCH ARTICLE

Open Access

Do we need to adjust for interim analyses in a Bayesian adaptive trial design?

Elizabeth G. Ryan*, Kristian Brock, Simon Gates and Daniel Slade

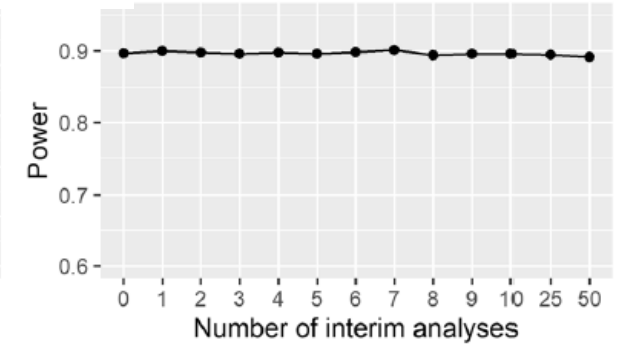
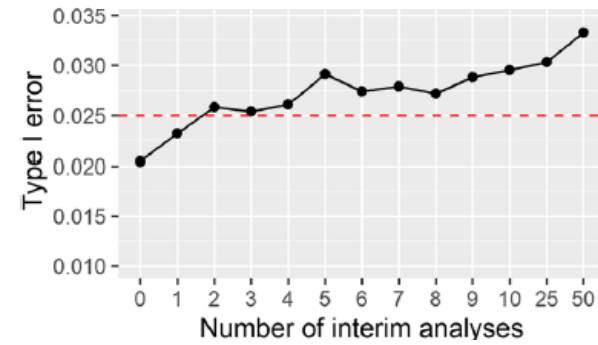


Birmingham
Cancer Research UK
Clinical Trials Unit

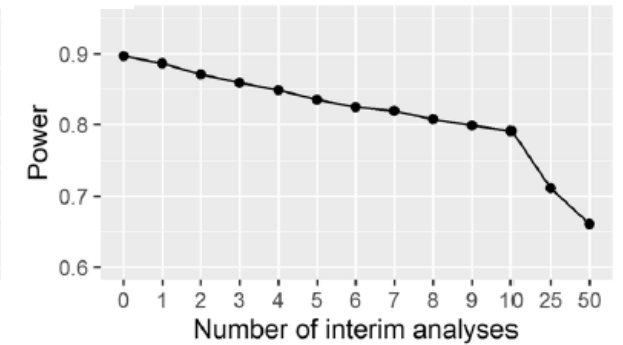
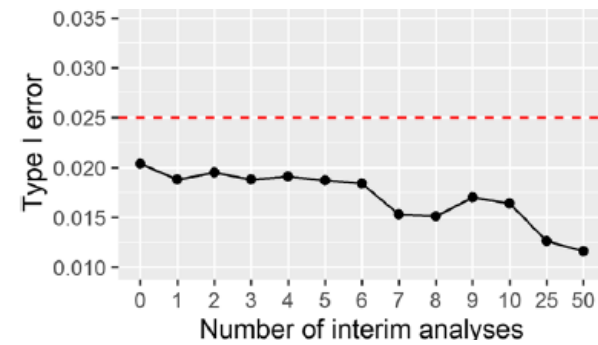


UNIVERSITY
BIRMINGHAM

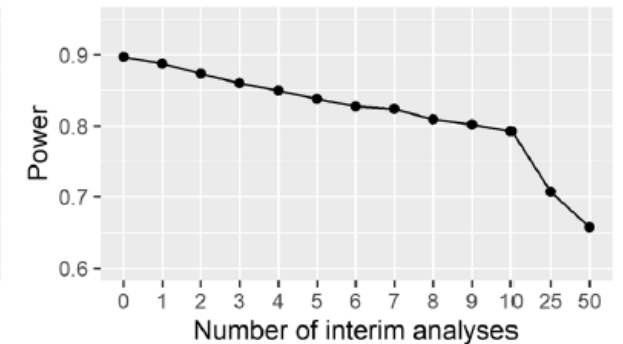
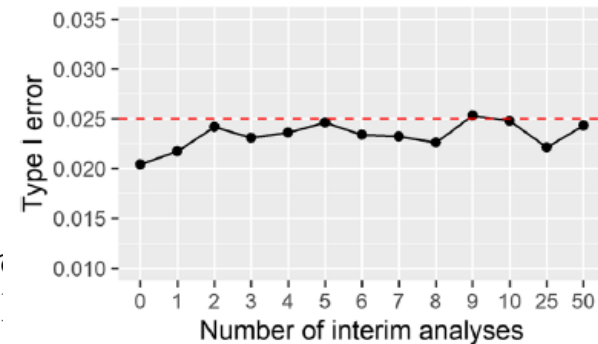
Early stopping for efficacy



Early stopping for futility



Early stopping for efficacy and futility



Bayesian analysis generates statistics that allow intuitive decision-making

- Bayesian final analysis
 - E.g. In Treatment Arm II, if trial gives **8 CRs out of 30 patients (28%)**
→ **$p(\text{true CR rate} > 20\%) = 0.85$**
 - 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 II, if trial gives **2 CRs out of 9 patients (26%)**
→ **$p(\text{GO decision at } n=15) = 0.24$**
 - 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



CANCER
RESEARCH
UK

Birmingham
Cancer Research UK
Clinical Trials Unit



UNIVERSITY OF
BIRMINGHAM

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 II, if trial gives **3 CRs out of 9 patients (36%)**
→ **$p(\text{true CR rate} > 20\%) = 0.88$**
- 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



CANCER
RESEARCH
UK

Birmingham
Cancer Research UK
Clinical Trials Unit



UNIVERSITY OF
BIRMINGHAM

Summary **Glo-BNHL**

- 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

'Fit-for-Filing' trial



Birmingham
Cancer Research UK
Clinical Trials Unit



UNIVERSITY OF
BIRMINGHAM

Bayesian Biostatistics Conference 2025

Using Bayesian Trial Designs to Change Clinical Practice in Rare Diseases

Lucinda Billingham

Professor of Biostatistics and Director of Biostatistics
Cancer Research UK Clinical Trials Unit
University of Birmingham



**CANCER
RESEARCH
UK**

Birmingham
Cancer Research UK
Clinical Trials Unit



**UNIVERSITY OF
BIRMINGHAM**

