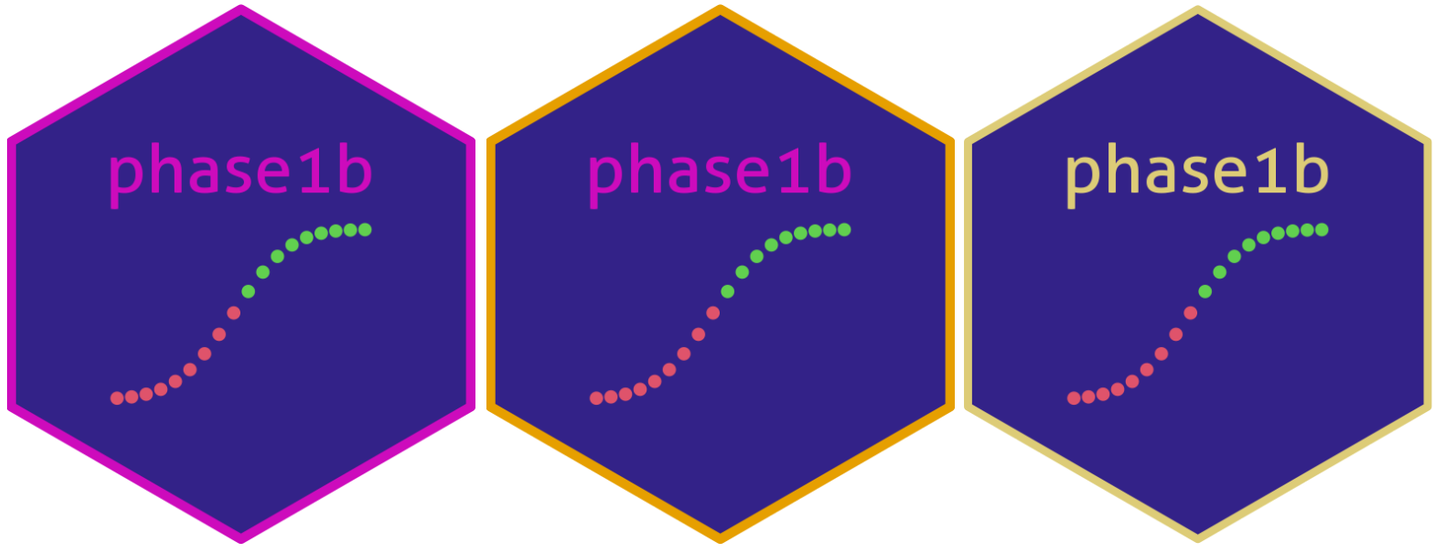
A Bayesian approach to decision making in early development clinical trials: An R solution

Audrey Yeo

Statisticians in Pharma Conference (PSI) 2024, Amsterdam, NL

This presentation has ALT text and as much as possible, uses colour-blind

Early oncology trials and why `phase1b`?



Prior and Posterior of Beta Distribution for response rate

- Conjugate Prior is $f(\pi)$, where $\pi \sim \text{Beta}(\alpha, \beta)$, same family of distribution of Posterior (see below)
- We know the mean response rate (RR) is :

$$\pi = \frac{\alpha}{\alpha + \beta}$$

- Likelihood is $f(x|\pi)$, where $x \sim \text{Binomial}(x, n)$
- The updated Posterior $f(\pi|x)$ is again a Beta distribution (same family as prior) :

$$\pi|\ x \sim \text{Beta}(\alpha + x,\ \beta + n - x)$$

where x is the number of responders of current trials

History and how to install :

- 2015 : Started as a need in Roche's early development group, package development led by Daniel Sabanés Bové in 2015.
- 2023 : Refactoring, Renaming, adding Unit and Integration tests as current State-of-Art Software Engineering practice.
- 100% written in R and Open Source.
- website : genentech.github.io/phase1b/

```
library(devtools)
devtools::install_github("https://github.com/Genentech/phase1b")
library(phase1b)
```

Use case:

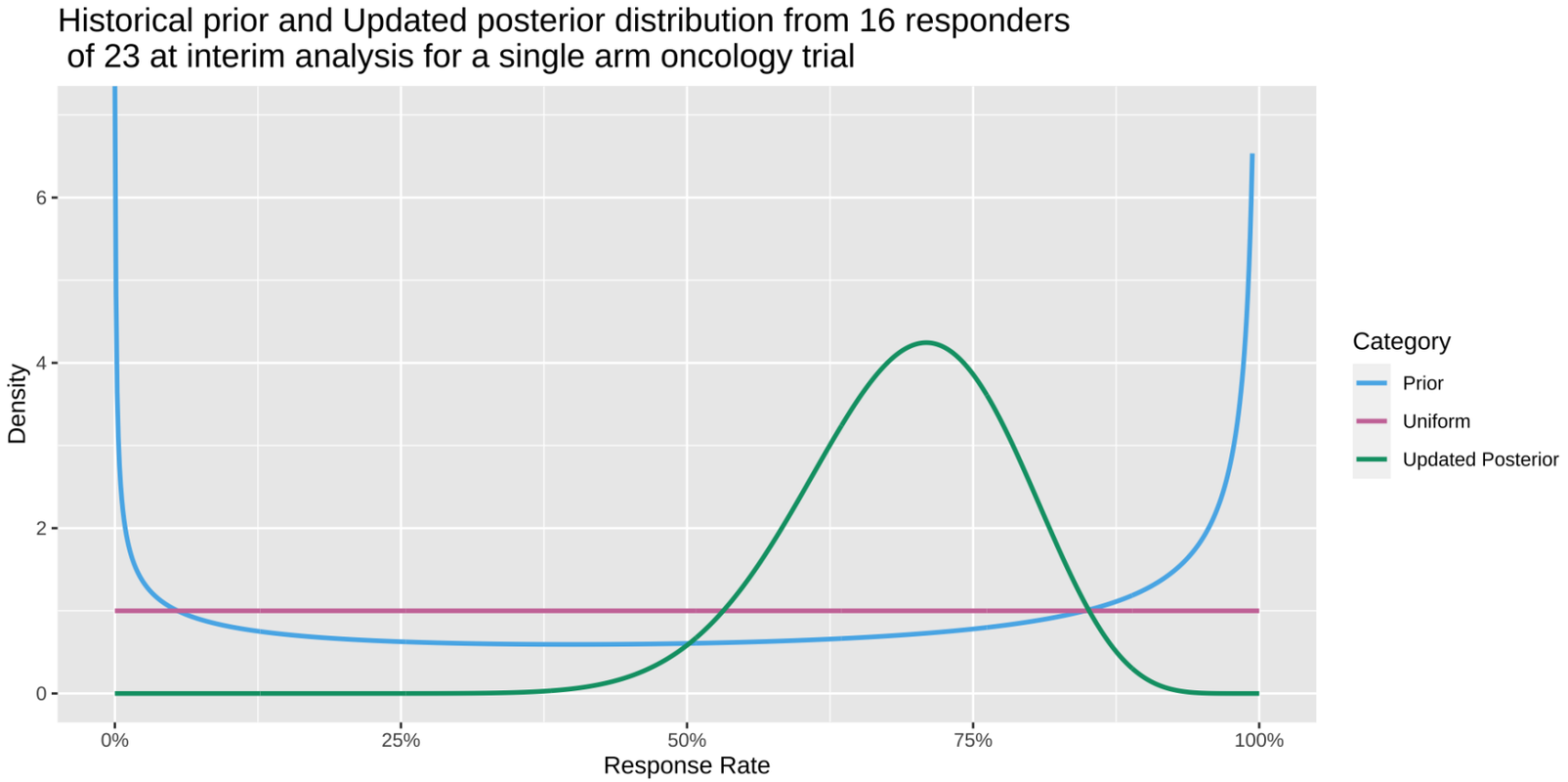
A single arm novel therapeutic with an assumed control response rate is at most 60%

Example	Interim	Final
Responders	16	23
n	23	40
Response rate	69.57 %	57.5 %
Posterior probability*	ask phase1b	ask phase1b
Predictive posterior probability*	ask phase1b	-
Decision to develop molecule further : Go/Stop/Grey Zone	ask phase1b	ask phase1b

* Posterior Probability : $P(\pi > 60\% | \alpha + n, \beta + n - x)$
* Predictive Posterior Probability : $P(\text{success or failure at final})$

Updating the Posterior and making a decision

- The updated Posterior will have the parameters $\alpha + x$ and $\beta + n - x$.
- With the prior of $\text{Beta}(0.6, 0.4)$ and the result of our interim results our Posterior has these parameters: $\text{Beta}(16.6, 7.4)$



`postprob()` example (Lee & Liu, 2008)

Example	Interim
Responders	16
n	23
Response rate	69.57 %
Standard of Care Response rate	60 %
Posterior probability	postprob( ) call from phase1b

```
1 postprob(x = 16, n = 23, p = 0.60, par = c(0.6, 0.4))
```

```
[1] 0.8359808
```

`predprob()` example (Lee & Liu, 2008), lower threshold

Example	Interim
Responders	16
n	23
Response rate (%)	69.57 %
Standard of Care Response rate (%)	60 %
Predictive Posterior probability	predprob( ) call from phase1b

```r
control = 0.6
thetaT_low = 0.6
result <- predprob(
  x = 16, n = 23, Nmax = 40, p = control, thetaT = thetaT_low,
  parE = c(0.6, 0.4)
)
result$result
```

```
[1] 0.9004913
```

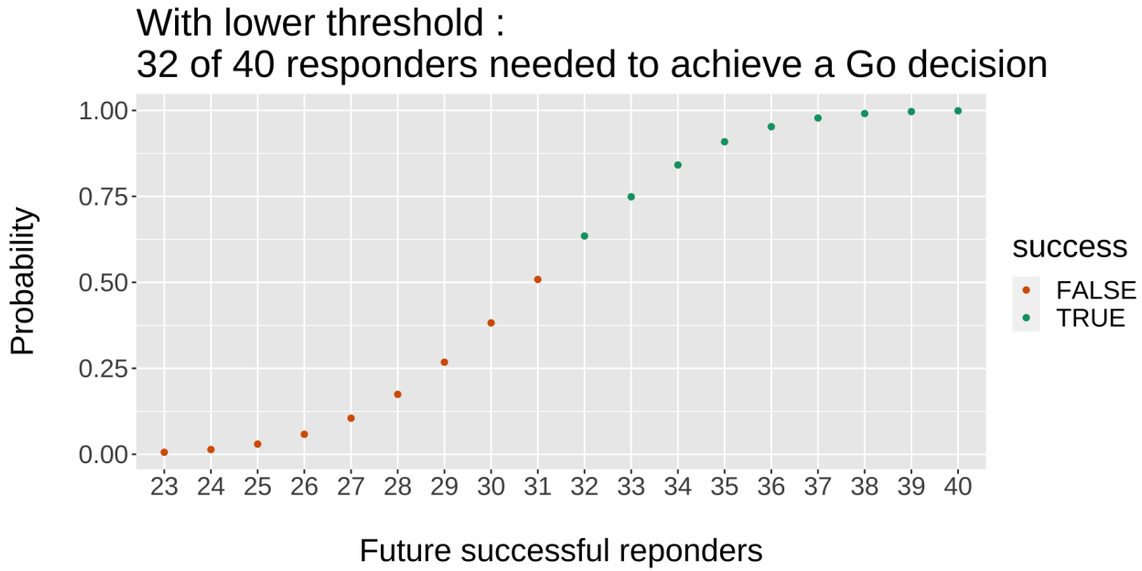
`predprob()` example (Lee & Liu, 2008), higher threshold

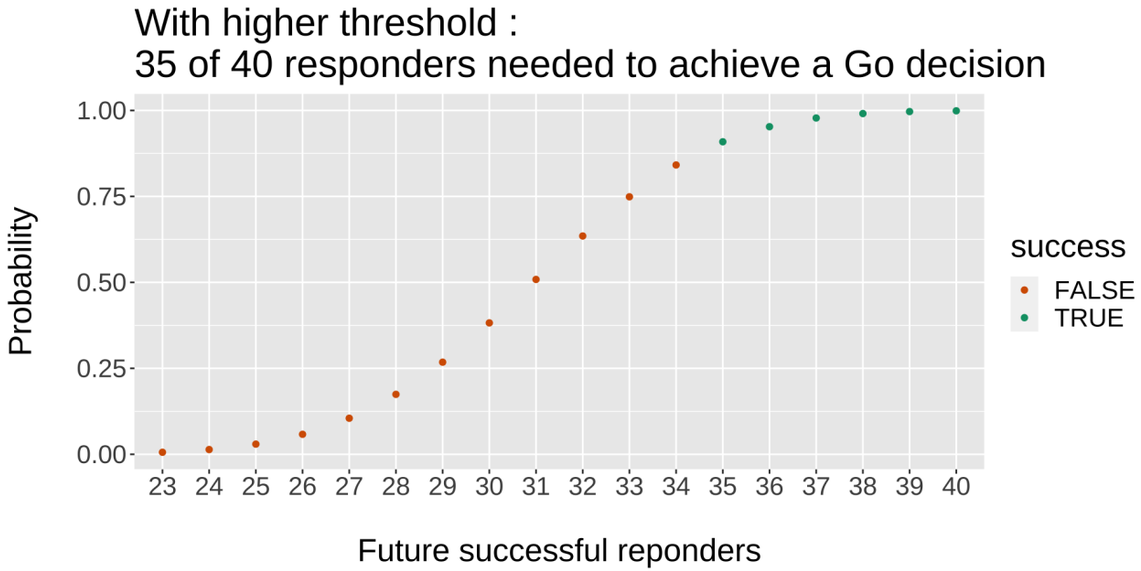
Example	Interim
Responders	16
n	23
Response rate (%)	69.57 %
Standard of Care Response rate (%)	60 %
Predictive Posterior probability	predprob( ) call from phase1b

```
thetaT_high = 0.9
result_high_thetaT <- predprob(
  x = 16, n = 23, Nmax = 40, p = control, thetaT = thetaT_high,
  parE = c(0.6, 0.4)
)
result_high_thetaT$result
```

```
[1] 0.5655589
```

Predictive Posterior Probability





(a) $\mathrm{P}(\theta_T > 0.6 |\ \text{data}) > 60\%$

(b) $\mathrm{P}(\theta_T > 0.6 |\ \text{data}) > 90\%$

Figure 1: Predictive Posterior CDF for different Efficacy Rules

Rules and Operating characteristics. A use case for `ocPostprob()`:

- Look for Efficacy: Go if $\mathrm{P}(\pi > 60\%) > 90\%$
- Look for Futility: Stop if $\mathrm{P}(\pi < 60\%) > 60\%$
- Prior of treatment arm $\mathrm{Beta}(0.6, 0.4)$.

```r
set.seed(2025)
res <- ocPostprob(
  nnE = c(20, 40), truep = 0.60, p0 = 0.60, p1 = 0.60, tL = 0.60, tU = 0.90, parE = c(0.6, 0.4),
  sim = 500, wiggle = TRUE, nnF = c(23, 40)
)
res$oc
```

```
  ExpectedN PrStopEarly PrEarlyEff PrEarlyFut PrEfficacy PrFutility PrGrayZone
1    30.384       0.546      0.112      0.082      0.142      0.506      0.352
```

Expanded features

…. and wiggle room!

	SOC uncertainty	single-arm	two-arm	simulation	plotting	boundaries
postprob		✓				
postprobDist	✓	✓				
predprob		✓				
predprobDist	✓	✓				
ocPostprob		✓		✓		
ocPostprobDist	✓	✓		✓		
ocPredprob		✓		✓		
ocPredprobDist	✓	✓		✓		
ocRctPostprobDist	✓	✓	✓	✓		
ocRctPredprobDist	✓	✓	✓	✓		
plotBeta				✓	✓	
plotDecision					✓	
plotOc					✓	
plotBounds					✓	
boundsPostprob						✓
boundsPredprob						✓

Concluding remarks

- Extension to other therapeutic areas that use response rate as endpoint if beta priors are appropriate
- Contact me to collaborate. Open issues here

References

- Thall P F, Simon R (1994), Practical Guidelines for Phase IIB Clinical Trials, Biometrics, 50, 337-349
- Lee J J, Liu D D (2008), A Predictive probability design for phase II cancer clinical trials, 5(2), 93-106, Clinical Trials
- Yeo, A T, Sabanés Bové D, Elze M, Pourmohamad T, Zhu J, Lymp J, Teterina A (2024). Phase1b : Calculations for decisions on Phase 1b clinical trials. R package version 1.0.0, https://genentech.github.io/phase1b
- Code for this presentation