Use of Probability of Success

A way to manage more available information

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Study design

- Sample size and Treatment arms
  - Two randomized parallel arms (New treatment vs Standard of care)
  - 1800 patients per arm
- Primary binary composite endpoint
  - Reach a predefined threshold for a biological endpoint
  - No severe adverse event directly linked to the drug administration
- $H_1 : \quad p_1 = 0.50 \quad \text{versus} \quad p_2 = 0.45 \qquad (p_1 - p_2 = 0.05)$
- Interim analysis
  - With 900 patients per arm (50% of planned sample size)
  - Pooled estimator & Overwhelming efficacy "stopping" rule
  - Updated PoS & Conditional Power are requested

Interim Analysis

Notations

Drug	Cohort 1 (before IA)	Cohort 2 (after IA)
New Trt	$\hat{p}_{11} = y_{11}/n_{11}$	$\hat{p}_{12} = y_{12}/n_{12}$
SoC	$\hat{p}_{21} = y_{21}/n_{21}$	$\hat{p}_{22} = y_{22}/n_{22}$

p_i is the true probability for group i (New treatment or Standard of Care)

Pooled estimator

$$\hat{p}_{IA} = \frac{y_{11} + y_{21}}{n_{11} + n_{21}} = \frac{n_{11} \times \hat{p}_{11} + n_{21} \times \hat{p}_{21}}{n_{11} + n_{21}} = 0.404$$

Overwhelming efficacy not reached

$$\hat{p}_{11} - \hat{p}_{21} < a \quad (a = 0.06^{1}) \Rightarrow \text{Which impact on PoS?}$$

[1] Nearly equivalent to p-value > 0.01 (two-sided).

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Distribution of interim estimators (1/2)

Constraints from the interim results

$$\begin{cases} \dfrac{n_{11} \times \hat{p}_{11} + n_{21} \times \hat{p}_{21}}{n_{11} + n_{21}} = \hat{p}_{IA} \\ \hat{p}_{11} - \hat{p}_{21} < a \end{cases}$$

$$\Rightarrow \begin{cases} \hat{p}_{21} = \dfrac{\hat{p}_{IA}(n_{11} + n_{21}) - n_{11}\hat{p}_{11}}{n_{21}} \\ \hat{p}_{21} > \hat{p}_{11} - a \end{cases}$$

$$\Rightarrow \frac{\hat{p}_{IA}(n_{11} + n_{21}) - n_{11}\hat{p}_{11}}{n_{21}} > \hat{p}_{11} - a$$

$$\Rightarrow \hat{p}_{11} < \hat{p}_{IA} + \frac{n_{21}}{n_{11} + n_{21}} \times a$$

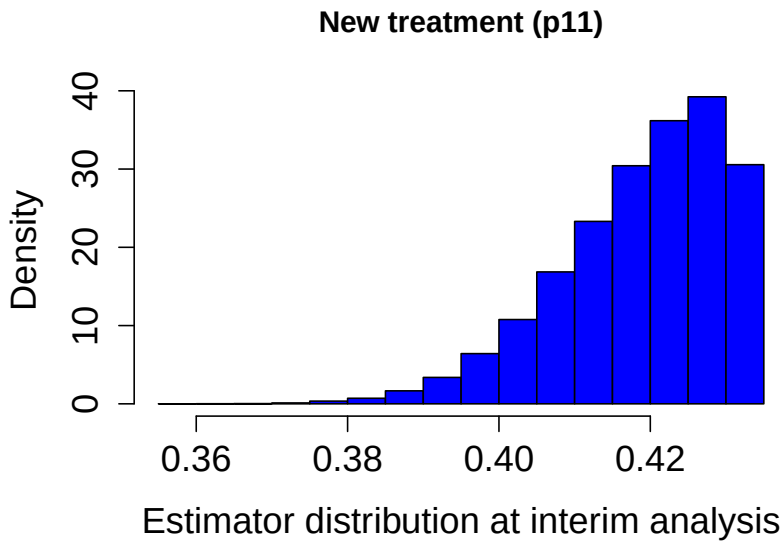
$\hat{p}_{21}$ is fully described by $(n_{11}, \hat{p}_{11}, n_{21}, \hat{p}_{IA})$

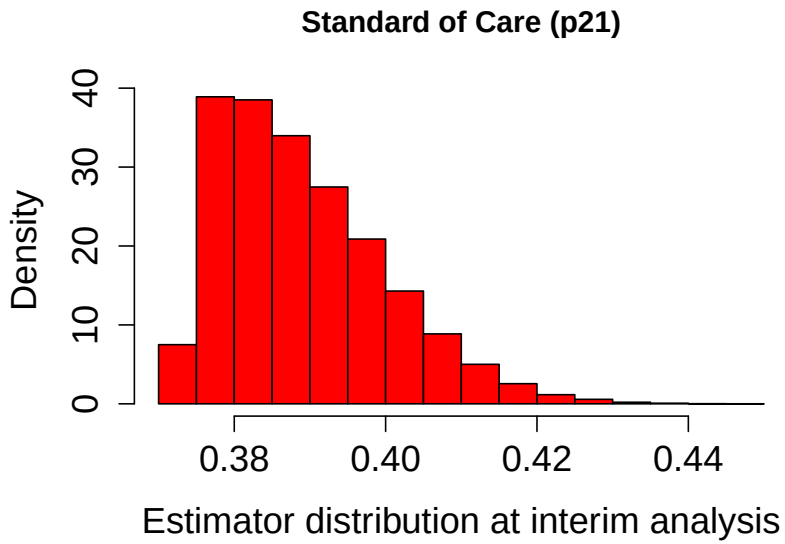
Distribution of interim estimators (2/2)

Conditional distributions (given p_1 and p_2)

$$\hat{p}_{11} \sim \mathcal{N}^{\left(p_1, \frac{p_1(1-p_1)}{n_{11}}\right)}_{\left[0, \hat{p}_{IA} + \frac{n_{21}}{n_{11}+n_{21}} \times a\right]}$$

$$\hat{p}_{21} | \hat{p}_{11} \sim \mathcal{D}irac\left(\frac{\hat{p}_{IA}(n_{11}+n_{21}) - n_{11}\hat{p}_{11}}{n_{21}}\right)$$

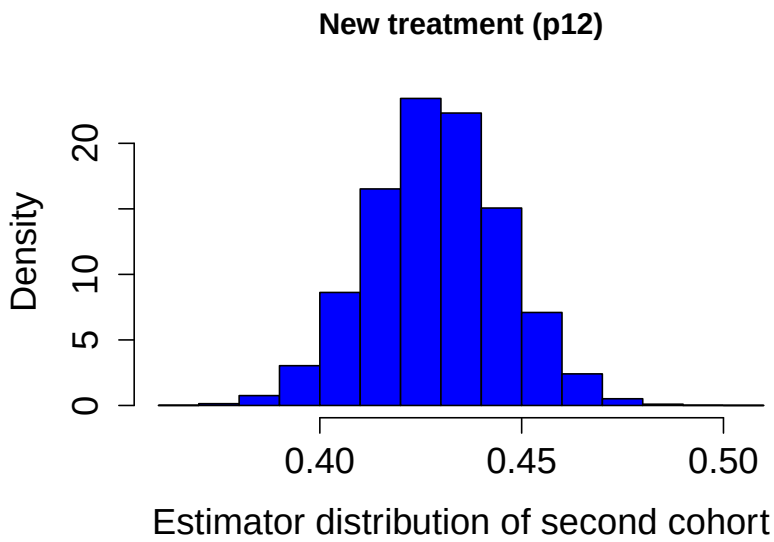


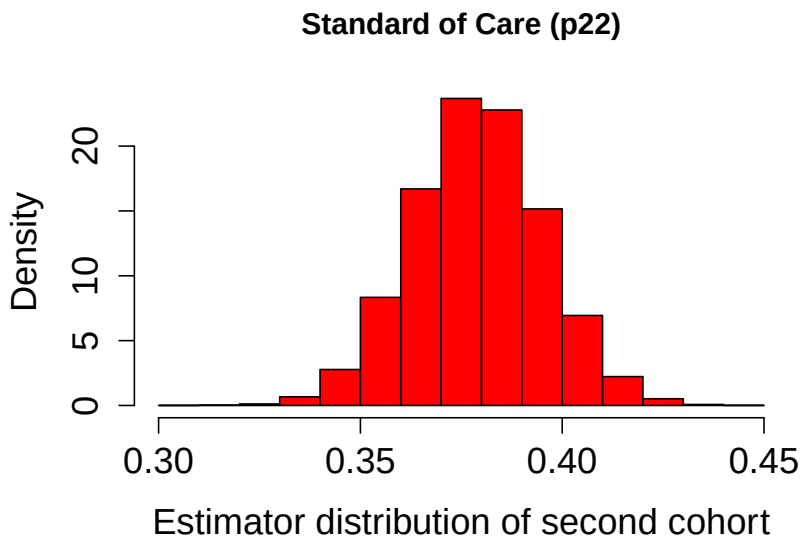


Distribution of second cohort estimators

Second cohort of patients (independent from first one)

- $\hat{p}_{12} \sim \mathcal{N}\left(p_1, \frac{p_1(1-p_1)}{n_{12}}\right)$ & $\hat{p}_{22} \sim \mathcal{N}\left(p_2, \frac{p_2(1-p_2)}{n_{22}}\right)$
- The estimator distributions remain unchanged due to cohort independence

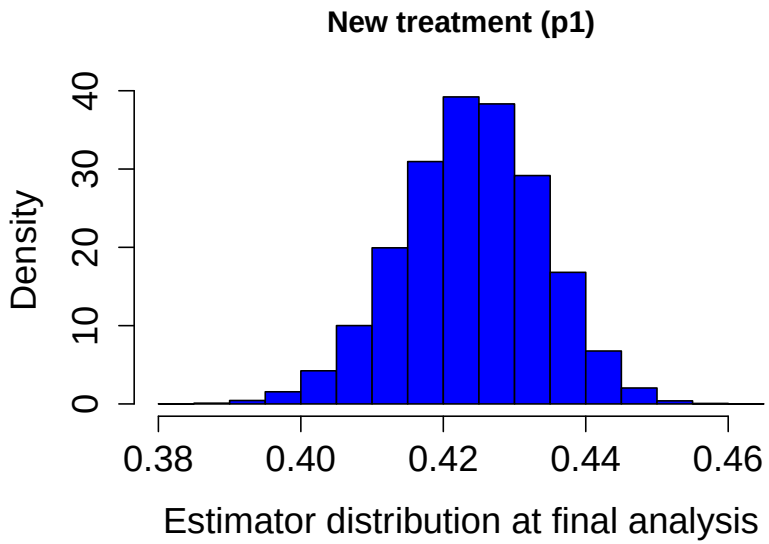


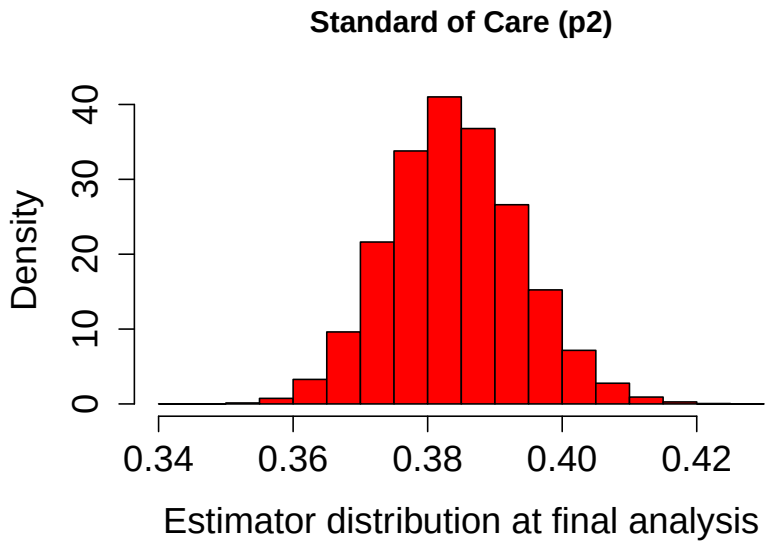


Distribution of final estimators

Distribution of final estimators

- $\hat{p}_i = \dfrac{n_{i1} \times \hat{p}_{i1} + n_{i2} \times \hat{p}_{i2}}{n_{i1} + n_{i2}}$
- Distributions are approximated by Monte Carlo
- Slightly asymmetric distributions





Conditional power

Conditional power

- Primary endpoint tested with a χ^2 test
- Conditional power = Probability of significant p-value

Application

- Adjusted $\alpha = 0.046$ at final analysis
- Condition power = 59.2%[a] (usually set to 90%, but 76% for this example)

[a] Approximated by 10^5 MC iterations.

Additional results

- Expected conditional mean of $p_1 - p_2 = 0.04$
- Expected conditional RR = 1.11
- Expected conditional OR = 1.18

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Available data

Previous clinical study

- New Treatment: 208 patient responses among 416 patients
- Standard of Care: 187 patient responses among 415 patients
- Usual way to take into account this information
  - Through the likelihood of observed data
  - Through an informative prior distribution

Interim Analysis

- Pooled estimator $\hat{p}_{IA} = 0.404$ (i.e. $y_{11} + y_{21} = 727$)
- Efficacy boundary $\hat{p}_{11} - \hat{p}_{21} < a \quad (a = 0.06)$
- Need a new method to take into account this information?

Likelihood of interim data (1/2)

Set of interim observations

$$(\hat{p}_{IA}, \hat{p}_{11} - \hat{p}_{21} < a) = \cup \left\{ (y_{11}, y_{21}) \;\middle|\; \frac{y_{11} + y_{21}}{n_{11} + n_{21}} = \hat{p}_{IA} \;\&\; \hat{p}_{11} - \hat{p}_{21} < a \right\}$$

Likelihood of interim data

$$[\hat{p}_{IA}, \hat{p}_{11} - \hat{p}_{21} < a | p_1, p_2] = \sum_{i=0}^{n_{11}} \sum_{j=0}^{n_{21}} [y_{11} = i | p_1][y_{21} = j | p_2] \times \mathbb{1}\left(y_{11} + y_{21} = 727^{a}\right) \times \mathbb{1}\left(\frac{y_{11}}{n_{11}} - \frac{y_{21}}{n_{21}} < a\right)$$

[a] Equivalent to $\hat{p}_{IA} = 0.404$ & $n_{11} + n_{21} = 1800$

Likelihood of interim data (2/2)

Likelihood of interim data (continued)

$$[\hat{p}_{IA}, \hat{p}_{11} - \hat{p}_{21} < a | p_1, p_2] = \sum_{i=0}^{727} [y_{11} = i | p_1][y_{21} = 727 - i | p_2] \times \mathbb{1}\left(\frac{i}{n_{11}} - \frac{727 - i}{n_{21}} < a\right)$$

- $[y_{11} = i|p_1]$ & $[y_{21} = 727 - i|p_2]$ are classic likelihood for a binomial model
- This likelihood can be combined with any other likelihood (mind the correlation!)
- This likelihood can be used by any inference algorithm

Inference (1/3)

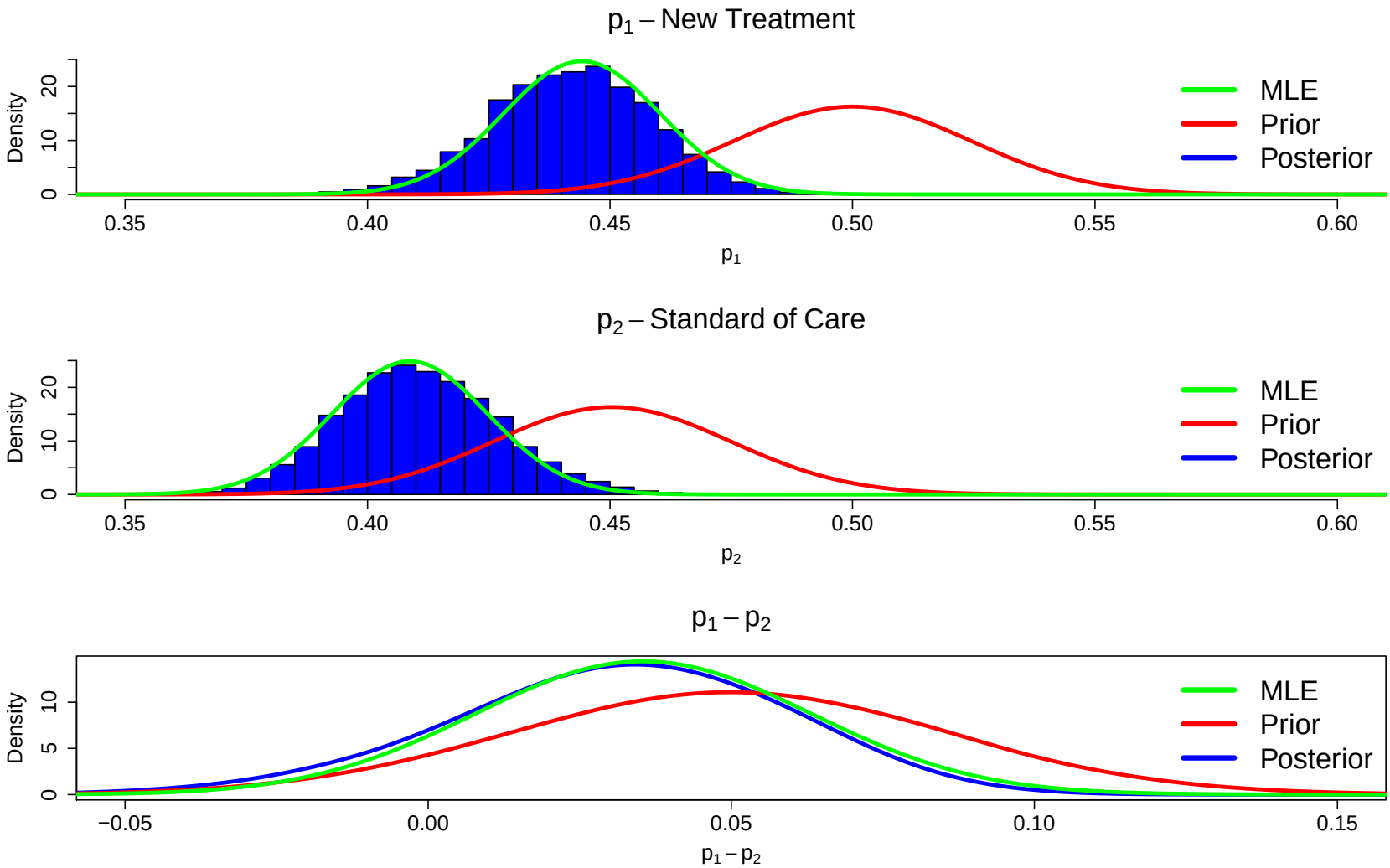
Frequentist inference

- The likelihood $[\hat{p}_{IA}, \hat{p}_{11} - \hat{p}_{21} < a | p_1, p_2]$ can be combined with the likelihood from the previous clinical study
- classic maximization algorithms can be applied
- Here a Nelder-Mead algorithm is used

Bayesian inference

- The likelihood from the previous clinical study can be used as a prior or as a part of the model likelihood (not both)
  - Both methods are equivalent due to Beta conjugate prior
- classic Bayesian algorithms can be applied
- Here a Sampling-Resampling algorithm is used

Inference (2/3)



Inference (3/3)

Parameter	Inference	Mean	Median	SD	CI95
p_1	MLE	0.444	0.444	0.016	[0.41;0.48]
	Prior	0.5	0.5	0.024	[0.45;0.55]
	Post.	0.442	0.442	0.017	[0.41;0.47]
p_2	MLE	0.409	0.409	0.016	[0.38;0.44]
	Prior	0.451	0.451	0.024	[0.4;0.5]
	Post.	0.411	0.41	0.016	[0.38;0.45]
$p_1 - p_2$	MLE	0.035	0.035	0.026	[-0.02;0.09]
	Prior	0.049	0.049	0.035	[-0.02;0.12]
	Post.	0.031	0.033	0.027	[-0.03;0.08]

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Exact method

Step 1: Model & assumptions

- $Y_1 \sim F_1(\theta)$ (Previous study)
- $Y_2 \sim F_2(\theta)$ (Current study)
- Posterior distribution $[\theta|Y_1]$

Step 2: Determine $f(\theta)$ assuming known θ

- Probability of a specific event (trial success, futility rule...)
- Here we use the conditional power of the study

Step 3: Assessment of θ uncertainty

$$\mathbb{E}_{\theta|Y_1}\left[f(\theta)\right] = \int_{\Theta} f(\theta)[\theta|Y_1]\mathrm{d}\theta$$

Approximate method

Integral calcultation

- Hard to perform
- Mainly feasible for conjugate prior-posterior distributions
- Need to use approximation methods

Monte Carlo approximation

- $(\theta^{(1)}, \ldots, \theta^{(M)})$ iid from $g(\theta)$

$$\mathbb{E}_{\theta|Y_1}\left[f(\theta)\right] = \int_{\Theta} f(\theta)[\theta|Y_1]\mathrm{d}\theta$$

$$\mathbb{E}_{\theta|Y_1}\left[f(\theta)\right] \approx \frac{1}{M}\sum_{m=1}^{M} \frac{f(\theta^{(m)})[\theta^{(m)}|Y_1]}{g(\theta^{(m)})}$$

- Convenient choice $g(\theta) = [\theta|Y_1]$

Application

Step 1: $[\theta|Y_1]$

- Posterior distribution of (p_1, p_2)
- Use prior distribution and interim analysis data

Step 2: $f(\theta)$

- $f(\theta)$ is the conditional power function (see Section 2)

Step 3: Probability of Success

- The Conditional Power is equal to 59.2%
- The PoS (approximated by Monte Carlo) is equal to 37.3%

Decision-making support

- Go/noGo decision about the next clinical study/step
- Anticipate workload for next step

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Conclusion

- Clinical results
  - Power 59.2% (usually set to 90%, but 76% for this example)
  - PoS 37.3% (61.8% before the study)
  - Combination of both decreased power & treatment effect lower than expected
- Reassess the (conditional) power and the PoS of your study
- Mind the difference between power and PoS
- Do not ignore any piece of information
- Mind the trade-off between the informativeness and the useness of the interim stopping rules
  - The more useful (i.e. believable) the rule is, the more informative it is
  - Double-edge sword! A useful stopping rule brings bad news if unreached

Conclusion

Thank you for your attention

Conclusion

BACKUP

Contents

Sampling-Resampling (1/4)

Objective

- Simulate values from a distribution defined by its density function $f(\theta)$

Principle

- Transform $f(\theta)$ into a discrete distribution
- Simulate from this discrete distribution

Hypotheses

- The discrete distribution is large and non-redundant

Sampling-Resampling (2/4)

Discretization (Sampling)

- Use an instrumental distribution g (easier to simulate than f)
- Simulate K values $\eta_k \sim g(\eta)$

Discrete probabilities

- For each value η_k, a weight can be expressed as $w_k = \frac{f(\eta_k)}{g(\eta_k)}$
- Each value η_k is associated with the probability $\omega_k = \frac{w_k}{\sum_{k=1}^{K} w_k}$

Final sampling (i.e. Resampling)

- Simulate K values $\theta_k \sim \mathit{Multinomial}(\{\eta_k\}_k, \{\omega_k\}_k)$

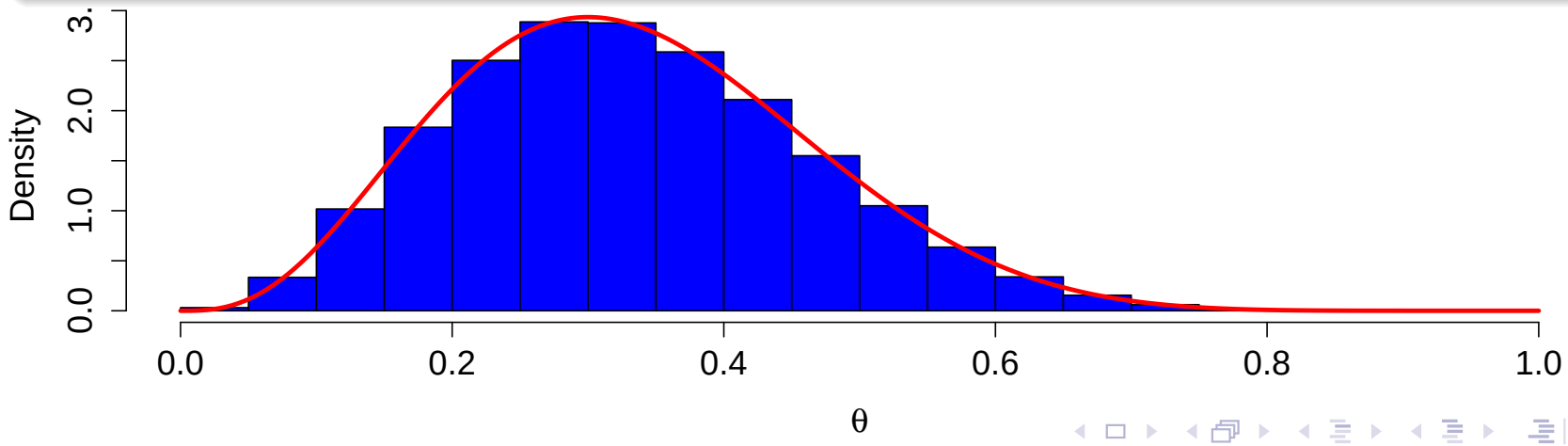
Sampling-Resampling (3/4)

Bayesian analysis

- Binomial model: 3 successes among 10 patients
- Prior: $\mathcal{B}eta(1,1)$, Posterior: $\mathcal{B}eta(4,8)$

Sampling-Resampling

- $f(\theta) = cste \times \binom{n}{y} \theta^y (1-\theta)^{n-y} \times 1$
- $g(\theta) = 1$ (Uniform distribution)



Sampling-Resampling (4/4)