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Current Issues in Randomized Controlled Trials

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Lecture 4: Bayesian Monitoring of Clinical Trials

Features:

- Combines subjective information about an unknown parameter (here, success rate) with the data in a formal way: Prior + Data = Posterior . . . or . . . Theory + Experience = Conclusion. Posterior distribution is used to make inferences about the unknown parameter.
- Works with the distribution of the unknown parameter of interest, not just with a fixed value.

Example: A phase 2 single-arm trial. (One sample)

To simplify the world, we'll reduce the range of the success rate from $0 \leq \pi \leq 1$ to just two possibilities:

Data	Parameter values	
	$\pi_0 = 0.50$	$\pi_A = 0.75$
Failure	a	b
Success	c	d

- When outcome is binary and choosing between two parameters, can express the relevant probabilities via terms used to assess a test's validity.

	Probability	Bayesian term	Validity term
Given:	$Pr\{H_A\}$	prior probability of π_A	prevalence
	$Pr\{Success \mid H_0\}$	a "likelihood"	1-specificity
	$Pr\{Success \mid H_A\}$	ditto	sensitivity
Find:	$Pr\{H_A \mid Success\}$	posterior probability of H_A	PPV

Method: Use Bayes Rule.

$$
\begin{aligned}
Pr\{H_A \mid Success\} &= \frac{Pr\{H_A, Success\}}{Pr\{Success\}} \\
&= \frac{Pr\{Success \mid H_A\} Pr\{H_A\}}{Pr\{Success\}} \\
&= \frac{Pr\{Success \mid H_A\} Pr\{H_A\}}{Pr\{H_A, Success\} + Pr\{H_0, Success\}} \\
&= \frac{Pr\{Success \mid H_A\} Pr\{H_A\}}{Pr\{Success \mid H_A\} Pr\{H_A\} + Pr\{Success \mid H_0\} Pr\{H_0\}} \\
&= \frac{Pr\{Success \mid H_A\} Pr\{H_A\}}{Pr\{Success \mid H_A\} Pr\{H_A\} + [1 - Pr\{Failure \mid H_0\}][1 - Pr\{H_A\}]} \\
&= \frac{\text{sensitivity} \times \text{prevalence}}{\text{sensitivity} \times \text{prevalence} + [1 - \text{specificity}] \times [1 - \text{prevalence}]} = \text{PPV}
\end{aligned}
$$

- In general, the posterior probability is a weighted average of the means of the prior distribution and the distribution of the data.
- The weights are the precisions with which the means are known. (Precision = 1/Variance)

Example: $H_0 : \pi \leq 0.50$ versus $H_A : \pi > 0.50$; point-alternative is $\pi_A = 0.75$.

Analysis of Patient 1:

Prior beliefs:

- $Pr\{\pi = 0.75\} = 0.50$
  → N.B. Each (of 2) possible parameter value in this example is equally likely; "open-minded" prior.

Data: Suppose response = success (data).

- $Pr\{Success|H_0 : \pi = 0.50\} = 0.50$ ...specificity → H_0 is true
- $Pr\{Success|H_A : \pi = 0.75\} = 0.75$ ...sensitivity → H_A is true

Calculate posterior probabilities:

$$Pr\{\pi = 0.75|Success\} = \frac{0.75 \times 0.50}{0.75 \times 0.50 + 0.50 \times 0.50} = 0.60 \text{ ...posterior probability of } S \rightarrow H_A$$

$$Pr\{\pi = 0.50|Success\} = 1 - Pr\{\pi = 0.75|Success\} = 0.40 \text{ ...posterior probability of } F \rightarrow H_0$$

	$\pi = 0.50$	$\pi = 0.75$	
Failure	0.50	0.25	*0.40*
Success	0.50	0.75	*0.60*
	0.50	0.50	

→ N.B. After obtaining data consistent with a higher value of π, posterior probability > prior probability.

Trials	Responders	$Pr\{\pi = 0.50\}$	$Pr\{\pi = 0.75\}$	Ratio
0	–	0.50	0.50	1.0
1	1	0.40	0.60	1.5

Analysis of Patient 2:

Prior beliefs:

- After Patient 1, "new" prior probability is $Pr\{H_A\} = Pr\{\pi = 0.75\} = 0.60$.

Data (i): *Another Responder* $\rightarrow$ more data consistent with H_A.

Calculate posterior probability of H_A:

$$Pr\{\pi = 0.75|S,S\} = \frac{0.75 \times 0.60}{0.75 \times 0.60 + 0.50 \times 0.40} = 0.692 \ldots \text{posterior probability of } S$$

	$\pi = 0.50$	$\pi = 0.75$	
Failure	0.50	0.25	*0.31*
Success	0.50	0.75	*0.69*
	0.40	0.60	

Trials	Responders	$Pr\{\pi = 0.50\}$	$Pr\{\pi = 0.75\}$	Ratio
0	–	0.50	0.50	1.0
1	1	0.40	0.60	1.5
2	2	0.31	0.69	2.2

Data (ii) *A Nonresponder* $\rightarrow$ data consistent with H_0.

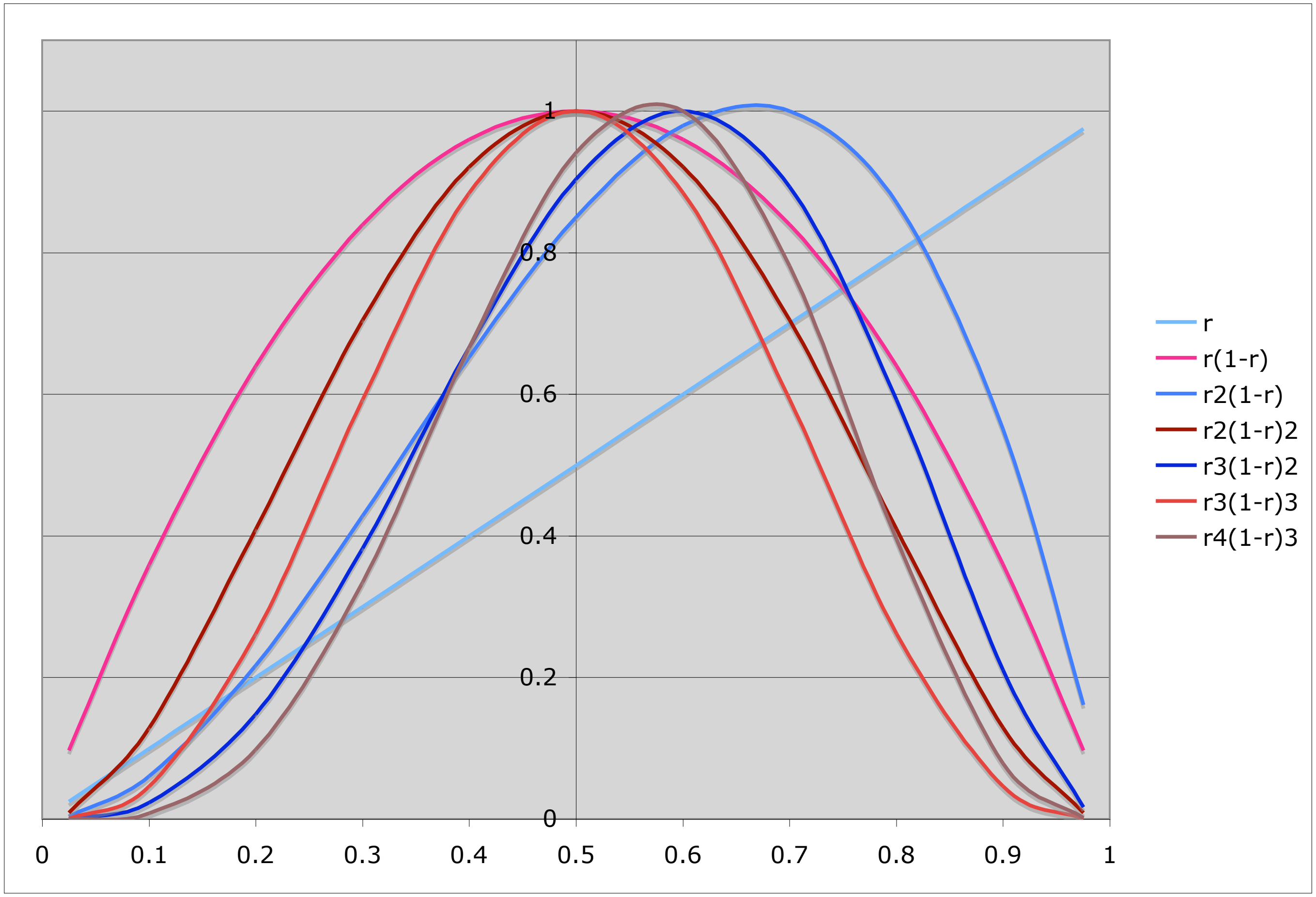
Calculate posterior probability of H_0:

$$Pr\{\pi = 0.75|S,F\} = \frac{0.25 \times 0.60}{0.25 \times 0.60 + 0.50 \times 0.40} = 0.429 \ldots \text{posterior probability of } S$$

	$\pi = 0.50$	$\pi = 0.75$	
Failure	0.50	0.25	*0.57*
Success	0.50	0.75	*0.43*
	0.40	0.60	

Trials	Responders	$Pr\{\pi = 0.50\}$	$Pr\{\pi = 0.75\}$	Ratio
0	–	0.50	0.50	1.0
1	1	0.40	0.60	1.5
2	1	0.57	0.43	0.75

Figure 1: A variety of prior distributions based on response rate $r = 0.50$, with increasing levels of precision, for $N = 1, ..., 7$.



ROBUSTNESS PRINCIPLE: In the presence of a lot of data, everyone will agree on the posterior distribution. *(Data outweigh prior.)*

Example 1, at the end of planned acrual: Sample size calculation called for $N = 33$ patients, expecting $S = 22$ responses.

- Given likelihood plus prior probabilities:
  - Prior: $Pr\{\pi = 0.75\} = 0.50$
  - Under H_0: $Pr\{S = 22|\pi = 0.50, N = 33\} \propto 0.50^{22}(1 - 0.50)^{11}$
  - Under H_A: $Pr\{S = 22|\pi = 0.75, N = 33\} \propto 0.75^{22}(1 - 0.75)^{11}$
- Calculate the posterior probability:
  - Under H_A: $Pr\{\pi = 0.75|N = 33, S = 22\} = \frac{[0.75^{22}0.25^{11}]0.50}{[0.75^{22}0.25^{11}]0.50 + [0.50^{33}]0.50} = \frac{[0.0823]0.50}{[0.0823]0.50 + [0.0225]0.50} = 0.785$
  - Under H_0: $Pr\{\pi = 0.50|N = 33, S = 22\} = 1 - 0.785 = 0.215$
  - Ratio $= 0.785/0.215 = 3.65$ implies that H_A is 3.65 times more likely than H_0 to hold.

Trials	Responders	$Pr\{\pi = 0.50\}$	$Pr\{\pi = 0.75\}$	Ratio
0	–	0.500	0.500	1.00
33	22	0.215	0.785	3.65

PREDICTIVE PROBABILITIES - Example 1, continued

Objective: Conduct an interim analysis when $N_1 \approx N/2$ to decide if/when the trial could be stopped.

(1) Find posterior probabilities of the parameters of interest, based on the data that occurred in Stage 1.

(2) Find probabilities of future outcomes conditional on parameter values of interest, and average the probabilities over the parameter values so that no particular value is assumed.

(3) Find posterior probabilities of the parameters of interest, based on all possible outcomes that *COULD OCCUR* in Stage 2.

Step 1: Analyze the data obtained thus far:

Calculate conditional likelihoods (for $\pi = 0.50$ and $\pi = 0.75$) based on observed set of data, $\{N_1 = 16, S_1 = 13\}$. Weight these via prior probabilities, to calculate the posterior probabilities:

- Under H_A: $Pr\{\pi = 0.75 | N_1 = 16, S_1 = 13\} =$
$$\frac{[0.75^{13} 0.25^3]0.50}{[0.75^{13} 0.25^3]0.50 + [0.50^{16}]0.50} = \frac{[0.2079]0.50}{[0.2079]0.50 + [0.0085]0.50} = 0.960$$

- Under H_0: $Pr\{\pi = 0.50 | N_1 = 16, S_1 = 13\} = 1 - 0.960 = 0.040$

- Ratio $= 0.96/0.04 = 24.3$ implies it is 24 times more likely that H_A is true.

Trials	Responders	$Pr\{\pi = 0.50\}$	$Pr\{\pi = 0.75\}$	Ratio
0	–	0.500	0.500	1.0
16	13	0.040	0.960	24.3

Step 2: Prior to additional Stage-2 accrual, consider all possible outcomes if accrue all N=33.

Calculate **future probabilities** ($Pr\{S_2 = s\}$) for the remaining $N_2 = 33 - 16 = 17$ patients (Col 4).

1. Generate conditional likelihoods (for $\pi = 0.50$ and $\pi = 0.75$) of all possible future outcomes; see Col 2 and Col 3.
2. Use posterior probabilities from Step 1 as weights – to average over the influences of π_0 and π_A while incorporating what was learned in Step 1; see Col 4.

$$
\begin{aligned}
Pr\{S_2 = s | N_2 = 17\} &= Pr\{S_2 = s | \pi = 0.75, N_2 = 17\} Pr\{\pi = 0.75 | S_1, N_1\} \\
&+ Pr\{S_2 = s | \pi = 0.50, N_2 = 17\} Pr\{\pi = 0.50 | S_1, N_1\}, \quad \text{for } s = 0, ..., 17.
\end{aligned}
$$

Col 1		Col 2		Col 3		Col 4		Col 5
p:		0.50		0.75		unkn		post'r, HA
S		Pr(S=s; p=)		Pr(S=s; p=)	Pr(S<=s)	Pr(S=s)	Pr(S<=s)	Pr(S=s)
0	1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0002
1	17	0.0001	0.0001	0.0000	0.0000	0.0000	0.0000	0.0006
2	136	0.0010	0.0012	0.0000	0.0000	0.0000	0.0000	0.0017
3	680	0.0052	0.0064	0.0000	0.0000	0.0002	0.0003	0.0050
4	2380	0.0182	0.0245	0.0000	0.0000	0.0007	0.0010	0.0148
5	6188	0.0472	0.0717	0.0001	0.0001	0.0019	0.0029	0.0432
6	12376	0.0944	0.1662	0.0005	0.0006	0.0042	0.0072	0.1192
7	19448	0.1484	0.3145	0.0025	0.0031	0.0082	0.0154	0.2887
8	24310	0.1855	0.5000	0.0093	0.0124	0.0162	0.0316	0.5491
9	24310	0.1855	0.6855	0.0279	0.0402	0.0341	0.0657	0.7851
10	19448	0.1484	0.8338	0.0668	0.1071	0.0701	0.1358	0.9164
11	12376	0.0944	0.9283	0.1276	0.2347	0.1263	0.2621	0.9705
12	6188	0.0472	0.9755	0.1914	0.4261	0.1857	0.4478	0.9900
13	2380	0.0182	0.9936	0.2209	0.6470	0.2129	0.6607	0.9966
14	680	0.0052	0.9988	0.1893	0.8363	0.1820	0.8427	0.9989
15	136	0.0010	0.9999	0.1136	0.9499	0.1091	0.9519	0.9996
16	17	0.0001	1.0000	0.0426	0.9925	0.0409	0.9928	0.9999
17	1	0.0000	1.0000	0.0075	1.0000	0.0072	1.0000	1.0000
Posterior probabilities:		0.0395		0.9605				

- N.B. $Pr\{S_2 = s\}$ is more variable than $Pr\{S_2 = s | \pi\}$ because it accounts for uncertainty in π.
- Incorrect approach: $Pr\{S_2 = s | \hat{\pi}\}$, where $\hat{\pi} = 13/16 = 0.81$. Problem: Accounts for uncertainty in future probabilities but not in $\hat{\pi}$.

Step 3: Calculate **posterior probabilities** (Col 5) for each of the possible outcomes that could occur.

$$Pr\{\pi = 0.75|S_2 = s\}$$
$$= \frac{Pr\{S_2 = s|r = 0.75\}Pr\{\pi = 0.75|S_1 = 13\}}{Pr\{S_2 = s|\pi = 0.50\}Pr\{\pi = 0.50|S_1 = 13\} + Pr\{S_2 = s|\pi = 0.75\}Pr\{\pi = 0.75|S_1 = 13\}},$$

for $s = 0, ..., 17$.

How can we use this information??

Approach 1:

- Find s such that $Pr\{\pi = 0.75|S \leq s\} \geq 0.95$, where 0.95 is desired level of confidence in future probabilities. According to Col 5, $S = S_1 + S_2 = 13 + 11 = 24$.

- Find $Pr\{S \geq 24|S_1 = 13, N_1 = 16, N = 33\}$. According to Col 4, this is $1 - 0.1358 = 0.864$. (The predicted probabilities of projected results, independent of π, are in italics below.)

Trials	Responders	$Pr\{\pi = 0.50\}$	$Pr\{\pi = 0.75\}$	Ratio
0	–	0.500	0.500	1.0
16	13	0.040	0.960	24.3
33	24	0.030	0.970	32.9
33	*24*	*0.136*	*0.864*	

- There is still a 14% chance that H_0 will be true. Stop the trial?

Approach 2: "Mix frequentist and Bayesian methods"

Use critical value from sample-size calculation to define α and $1-\beta$:

- Design stage:
  - If $Pr\{S \geq 22|\pi = 0.50, N = 33\} = 0.040 \equiv \alpha$ (analog of Col 2, cumulative version, at $S_1 + S_2 = S = 11 + 13$, but no interim analysis)

  - Then $Pr\{S \geq 22|\pi = 0.75, N = 33\} = 0.901 \equiv 1-\beta$ (analog of Col 3, cumulative version)

- At this critical value (i.e., $S = 22$), the predicted probability based on interim data (independent of π; analog of Col 4, cumulative version): $Pr\{S \geq 22|N = 33\} =$ *0.968*.

* * * * *

Berry's comment:

- Frequentist interim analyses require overall $\alpha > 0.05$ to achieve final $\alpha \leq 0.05$ because H_0 assumed true.
- Bayesian analyses aren't penalized because no particular π is assumed.