Bayesian Clinical Trials
D.A. Berry (2006)
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Growing interest in Bayesian methods

Why?

- Goal to improve drug and medical device development inside and outside of clinical trials (costs, treatment effectiveness)
- Berry argues the Bayesian approach provides a better perspective and more efficient approach to accomplish the desired improvements

Role in research

- In 2006, 10% of medical device approvals by the FDA were based on Bayesian designs and analyses

Frequentist vs. Bayesian approach

Let us define a parameter *p* as the proportion of successes in a greater population of experimental units.

FREQUENTIST

- Parameters (i.e. *p*) are fixed
- P-values and inferences depend on trial design and investigators' intentions
- Failure to specify a stopping rule in advance or to follow protocol results in no possible conclusion
- *P*-value = the probability of observing a result as or more extreme than that observed assuming that the treatment is ineffective

Frequentist vs. Bayesian approach

Let us define a parameter *p* as the proportion of successes in a greater population of experimental units.

BAYESIAN

- Knowns taken as givens, all unknowns (i.e. *p*) subject to a probability distribution
- Posterior probability depends on prior
- All Bayesian inferences based on current distribution of unknown parameters & can be made at any time
- Posterior probability = the probability that the therapy is ineffective

Frequentist vs. Bayesian approach

Classical Example 1:

design of exactly 10 observations, 7 successes observed (SSFSSFSSSF)

Probabilities arise from a binomial pmf with size = n = 10 and prob =*p*

Successes	0	1	2	3	4	5	6	7	8	9	10
$p = 0.35$	0.013	0.072	0.176	0.252	0.238	0.154	0.069	**0.021**	0.004	0.001	0.000
$p = 0.70$	0.000	0.000	0.001	0.009	0.037	0.103	0.200	**0.267**	0.233	0.121	0.028

Figure 1 | **Probabilities for a hypothetical clinical trial.**

Frequentist vs. Bayesian approach

Classical Example 1:

design of exactly 10 observations, 7 successes observed (SSFSSFSSSF),

H0: $p = 0.35$

Classical 2-sided *P*-value for P(X = 7):

P(X=0) + P(X=7) + P(X=8) + P(X=9) + P(X=10) = 0.039

Successes	0	1	2	3	4	5	6	7	8	9	10
$p = 0.35$	0.013	0.072	0.176	0.252	0.238	0.154	0.069	**0.021**	0.004	0.001	0.000
$p = 0.70$	0.000	0.000	0.001	0.009	0.037	0.103	0.200	**0.267**	0.233	0.121	0.028

Figure 1 | **Probabilities for a hypothetical clinical trial.**

Frequentist vs. Bayesian approach

Classical Example 2:

design where experiment continues until until 3 failures observed, 10 observations made (SSFSSFSSSF)

Probability now arises from negative binomial pmf

Classical *P*-value for P(10 obs, 3 failures, $p = 0.35$) = 0.004

- Much smaller *P*-value compared to Example 1 (*P*-value = 0.039) with the same results

Frequentist vs. Bayesian approach

Takeaways about frequentist approach:

- Evidence against the null hypothesis varies based on trial design
- Trial design cannot be altered after it is in progress
- Cannot deviate from stopping rule

Frequentist vs. Bayesian approach

Bayesian Example:

We obtain the same data (SSFSSFSSSF) and consider two possible probabilities for *p*: 0.35 and 0.70

- Consider only the probabilities of observed results
- If we assume both values are equally likely *a priori*:
  - prior probability of 0.35 = 0.50
  - posterior probability of 0.35 = Bayes factor = 0.021/(0.267+0.021) = 0.073

Successes	0	1	2	3	4	5	6	7	8	9	10
$p = 0.35$	0.013	0.072	0.176	0.252	0.238	0.154	0.069	**0.021**	0.004	0.001	0.000
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Figure 1 | **Probabilities for a hypothetical clinical trial.**

Bayesian approach

- Start with flat prior
- Each data point updates probability distribution
- Probability distribution becomes more narrow and peaked
- Can calculate posterior probability if trial stops early

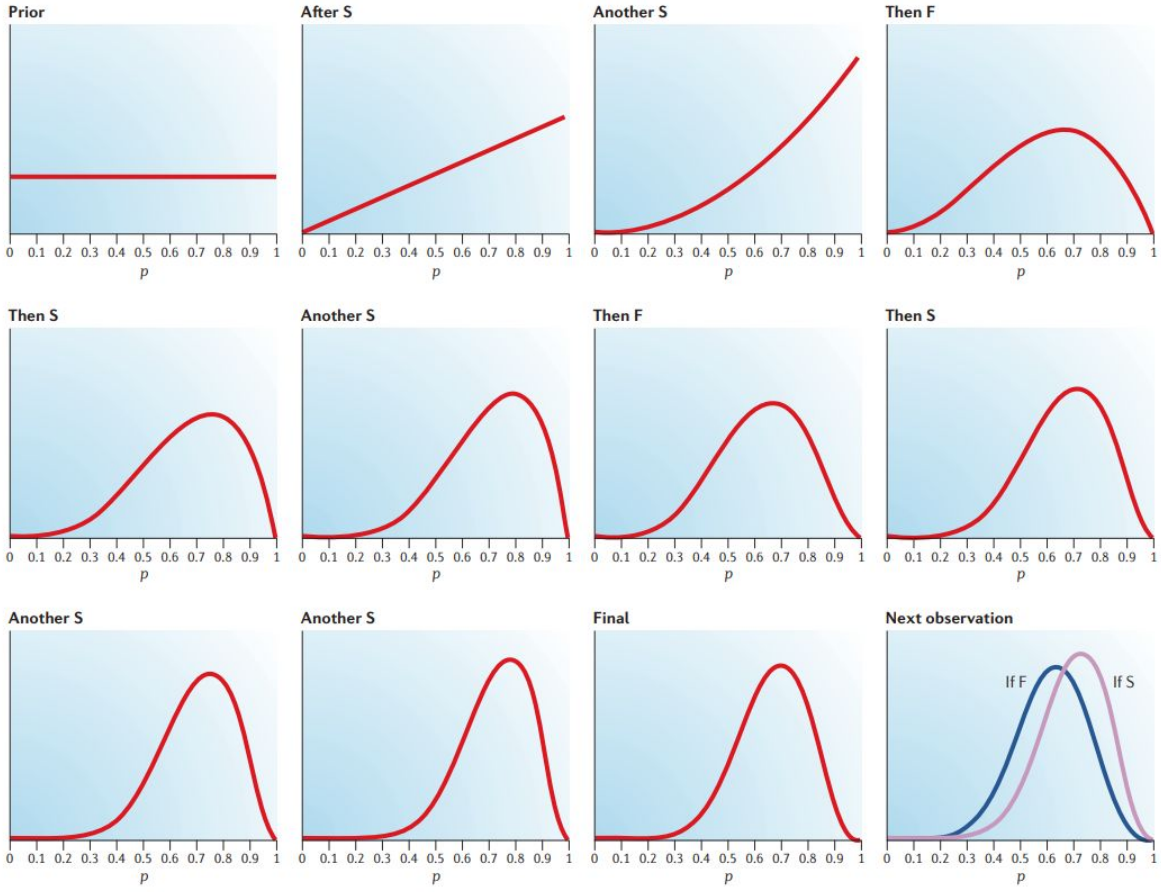
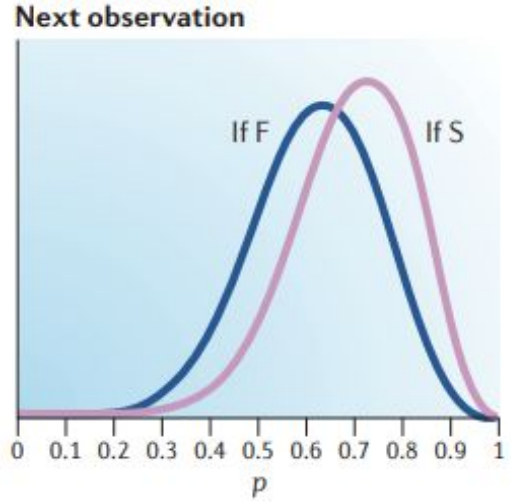


Figure 2 | **Sequence of probability distributions for success rate *p* corresponding to data SSFSSFSSSF.** The prior

Predictive probabilities and trial design

Example: Using the same example trial of 10 patients, will the treatment be successful for the next (11th) patient?

We must combine two sources of uncertainty to calculate the predictive probability of success for the next patient:
1) the inherent chance *p* of success/failure
2) the probability distribution of *p*



Predictive probabilities and trial design

Application of Bayesian predictive probabilities: monitoring clinical trials

Example of application of Bayesian analysis in conjunction with frequentist trial design:
Phase II neoadjuvant HER2/*neu*-positive breast cancer trial at M.D. Anderson Cancer Center

Target accrual: 164 patients, 2 treatment arms (chemo w/ and w/o trastuzumab)

Primary endpoint: pathological complete response (pCR) of tumor

Predictive probabilities and trial design

Example of application of Bayesian analysis in conjunction with frequentist trial design (continued):
Phase II neoadjuvant HER2/*neu*-positive breast cancer trial at M.D. Anderson Cancer Center

- Slower than expected accrual
- DSMB assessed available results when 34 patients had data available, requested Bayesian predictive probability of frequentist statistical significance when 164 patients had been treated
- High probability (of what?) + ethics of continued randomization led to overriding trial protocol (to do what?)

Adaptive Designs

An **adaptive design** modifies the probability of of subject getting new or old treatment based on the treatments' performances in a given experiment

Pros:

+ more effective than standard designs at identifying 'the right dose' or 'the better treatment'
+ many more doses can be considered in an adaptive design, even though some may be little used or even never used
+ better treatment assigned to more patients based on results

Adaptive Designs

Modifications possible in Bayesian approach:

- stopping the trial at any point based on results
- adaptive assignment of patients to treatments based on results
- adding/dropping treatment arms based on effectiveness in results
- extending accrual beyond original target to get a more satisfactory conclusion or answer

Takeaways

- **Bayesian approach in the context of medical device and drug development allows gradual updating of knowledge at any time without penalty**
- **Bayesian approach in clinical trials is directly tied to decision making (i.e. predictive probabilities)**
- **Bayesian approach to adaptive designs allows for increased flexibility, more informative and smaller trials, and better treatment for enrolled patients**