Bayesian Approaches to Evaluating Clinical Trial Data: An Overview

Joel B. Greenhouse
Department of Statistics
Carnegie Mellon University
joel@stat.cmu.edu

Setting and Terminology

Treatment Effect (TxEffect)

Eg. Median Years of Survival Gained using A vs B

(B can be either a placebo or active comparator)

Goal: To reach consensus about TxEffect

Source of Evidence: Randomized Controlled Trial (RCT)

H_o: TxEffect = 0

H_a: TxEffect > 0

Measure of Evidence: Conventional Analysis

P-value = Probability of the observed RCT TxEffect (or one more extreme), assuming H_o i.e., no treatment effect

Setting and Terminology (con’t)

Bayesian Perspective:

How does the current RCT change our opinion about the TxEffect?

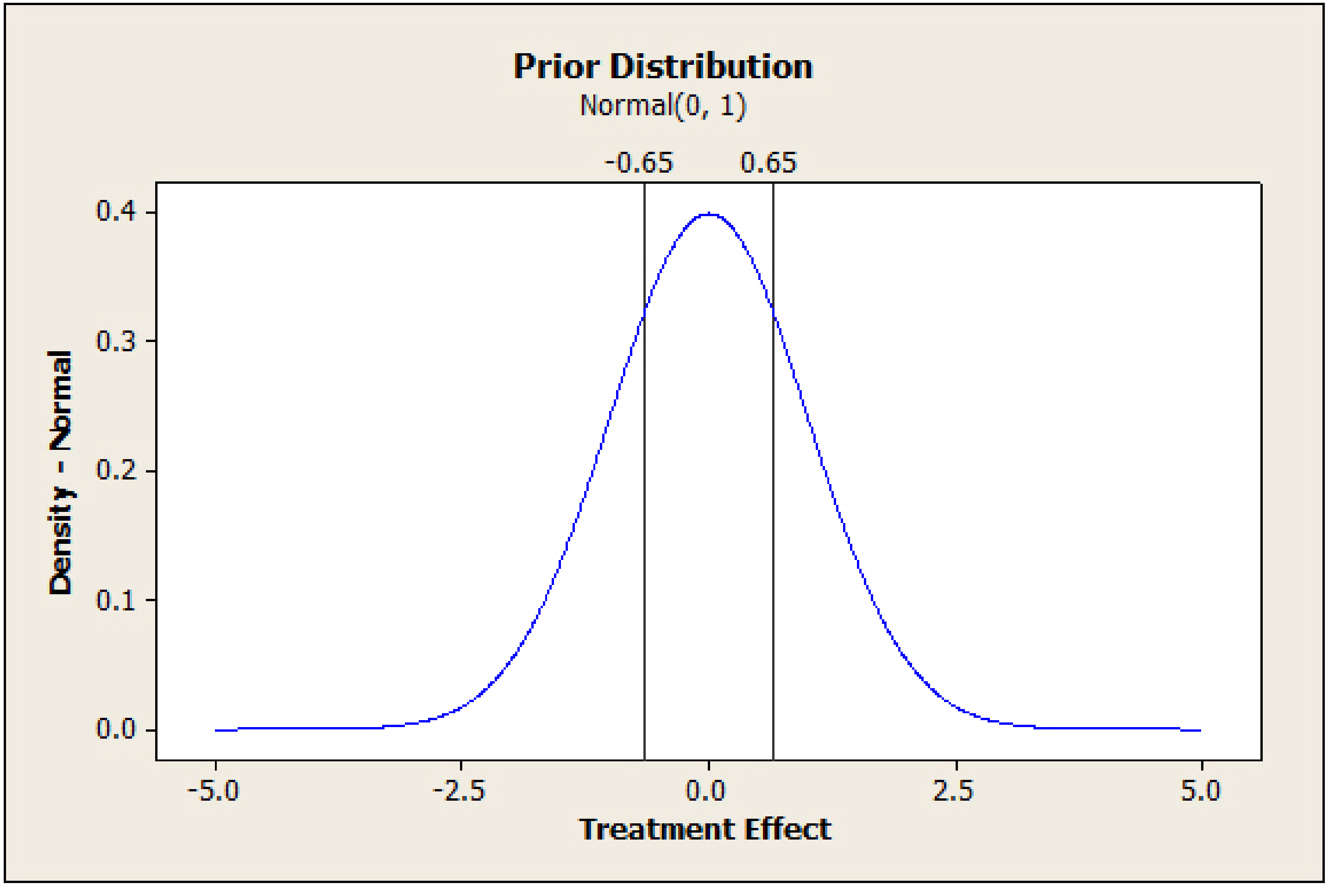
Probabilistic Approach

- A reasonable assessment of the plausible values of the TxEffect (excluding the evidence from the RCT) – Prior Distribution
- Support for the different values of the TxEffect based solely on data from the RCT – Likelihood

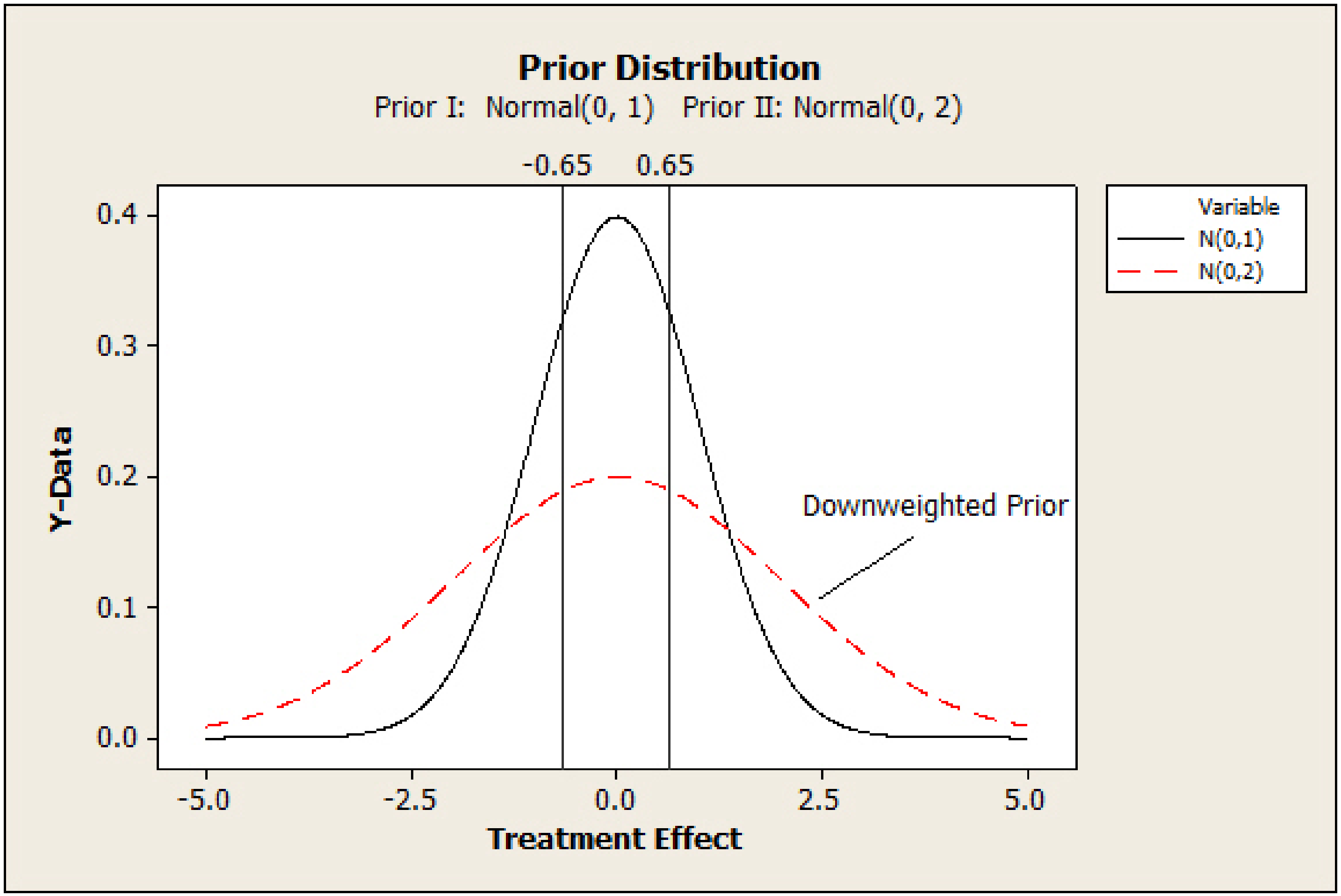
Measure of Evidence

- A combination of historical assessment about the TxEffect with the RCT information to form the current opinion about the TxEffect – Posterior Distribution

Prior I: Centered = No TxEffect
Probability[.5 < RR < 1.9] = 0.5



Prior II: Centered = No TxEffect
Probability[.22 < RR < 3.4] = .50



Prior Specification

Using Historical Information

A. Irrelevant

B. Equal

- Individual patients are exchangeable
- Pool studies

C. Equal but Discounted

- Previous studies may not be directly related
- We want to discount their influence
- Downweight, e.g., reduce effective prior sample size

For Monitoring

D. Skeptical Prior

- Expresses skepticism about hypothesized treatment effects
- Reasonable expression of doubt
- Protection from early stopping for positive effects

E. Enthusiastic Prior

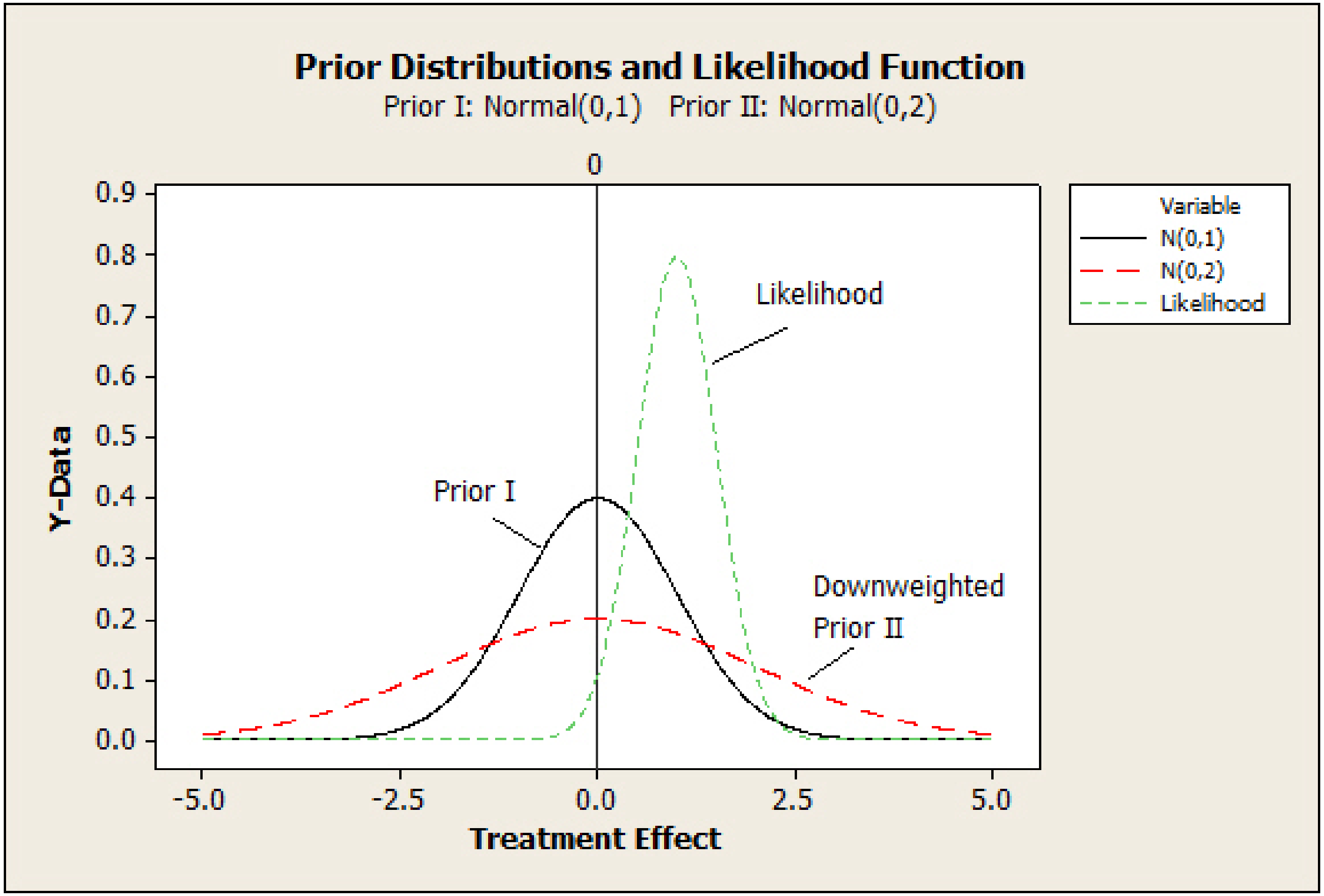
- Counterbalance to the skeptical prior
- Conservative with respect to early negative effects

Bayesian Approach

Bayes Rule tells us how to combine the Prior Distribution with the Likelihood to find the Posterior Distribution

Prior x Likelihood → Posterior

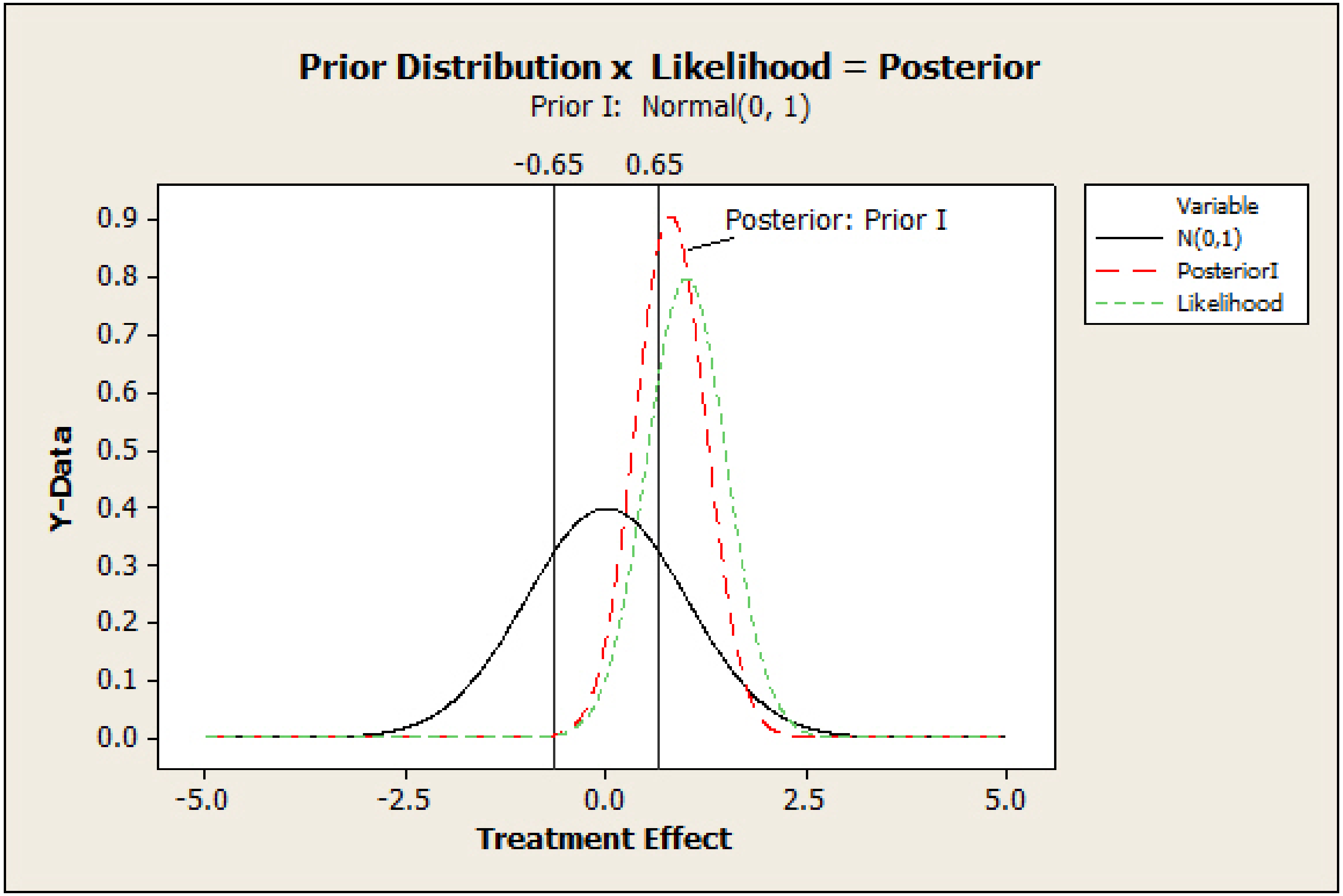
Prob weights for TxEffect based on other sources, eg, historical info expert consensus	**X**	Support for diff values of TxEffect based on current RCT



Prior Distributions and Likelihood Function
Prior I: Normal(0,1)   Prior II: Normal(0,2)
0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Y-Data
Likelihood
Prior I
Downweighted
Prior II
-5.0
-2.5
0.0
2.5
5.0
Treatment Effect
Variable
N(0,1)
N(0,2)
Likelihood

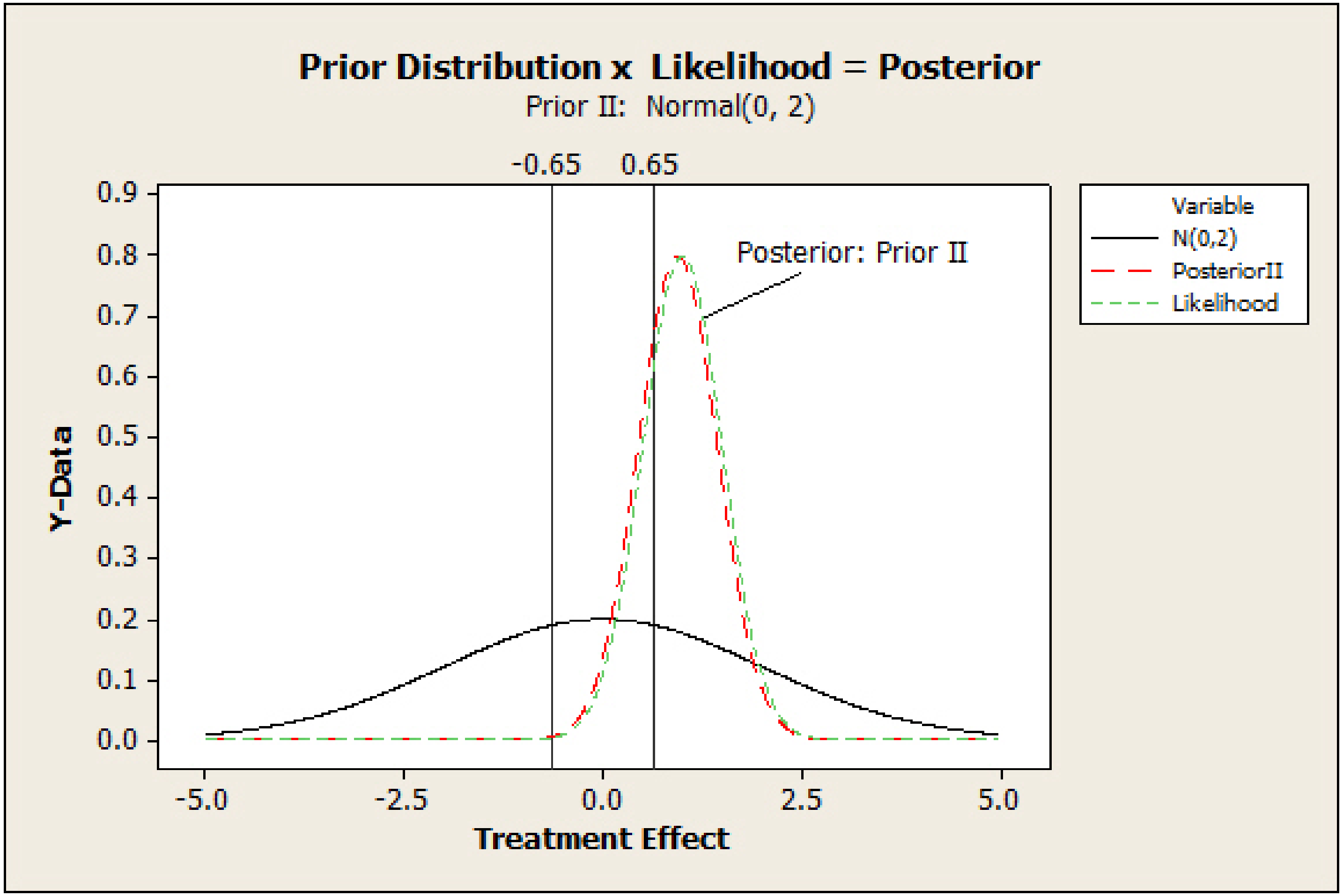
Example: Bayes Rule I

Prob(TxEffect > 0 |data) = 0.97



Example: Bayes Rule II

Prob(TxEffect > 0 |data) = 0.98



Case Study

Selected References
Bayesian Methods for Analyzing RCT Data in Practice

- Greenhouse JB and Seltman H (2005). Using prior distributions to synthesize historical evidence: Comments on the Goodman-Sladky case study of IVIg in GBS. *Clinical Trials*, 2(4):311-318.

- Kass R and Greenhouse JB (1989). Comment on “Investigating therapies of potentially great benefit: ECMO” by J. Ware. *Statistical Science,* 4:31-37.

- Spiegelhalter DJ, Abrams KR and Myles JP (2004). *Bayesian approaches to clinical trials and health care evaluation.* Chichester, England: John Wiley & Sons.

Some Topics for Further Discussion

I. There is a natural concern that the posterior inferences may be sensitive to the choice of prior distribution
   - **Sensitivity Analysis:** Instead of specifying a single prior distribution consider a family of priors and see how much the posterior inferences change as the prior varies over this family.

II. What is the role for non-RCT sources of evidence to help inform FDA about questions of effectiveness and safety?

Thank You

Case Study: Guillain-Barré Syndrome (GBS)

Background

- Immune system attacks part of the peripheral nervous system
- First affects the legs, moving upward
- The point of greatest weakness or paralysis occurs days or weeks after the first symptoms occur
- Recovery may be as little as a few weeks or as long as a few years
- Median time to regain ambulation: **80 to 110 days**

Treatments

- **Plasma Exchange (PE)** - whole blood removed; red and white blood cells are separated from the plasma; then reinfused.
- **Intravenous Immune Globulin (IVIg)** - intravenous injections of proteins that appear to lessen the immune attack on the nervous system

Case Study: Guillain-Barré Syndrome (con't)

Outcome

- Time to unaided walking (days)

Evidence for Efficacy

- RCT: PE > Placebo (37% reduction in median time to walking)
- RCT: IVIg **?** PE

Range of Equivalence: ± 14 days

Case Study

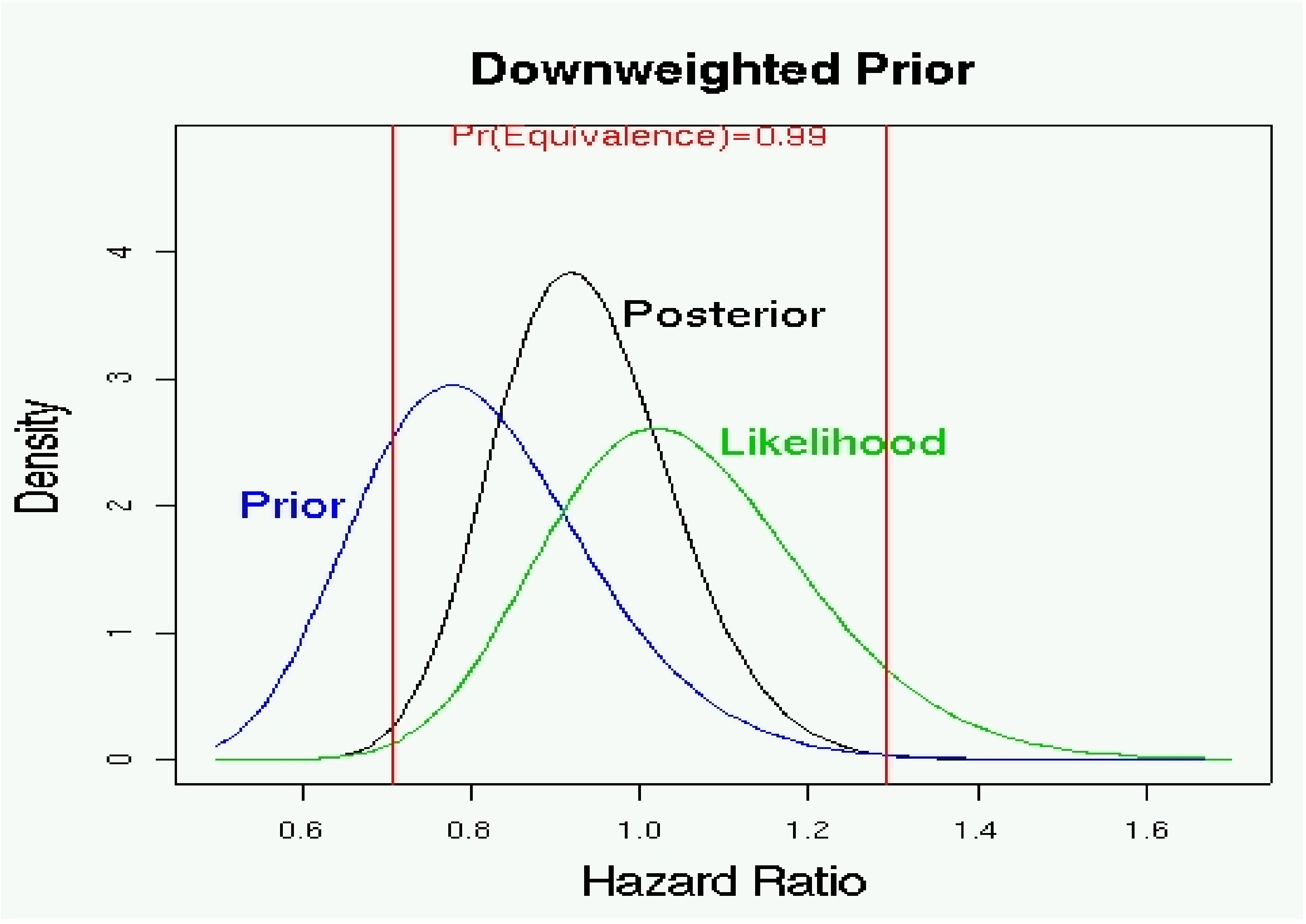
Earlier Study: Van der Merche, *NEJM* 1992

Treatment	Median Time to Walking (days)	Sample Size
IVIg	55 days	N = 74
PE	69 days	N= 73
Hazard Ratio (HR)	**55/69 = 0.80** (CI: 0.62 – 1.02)	(p-value = 0.07)

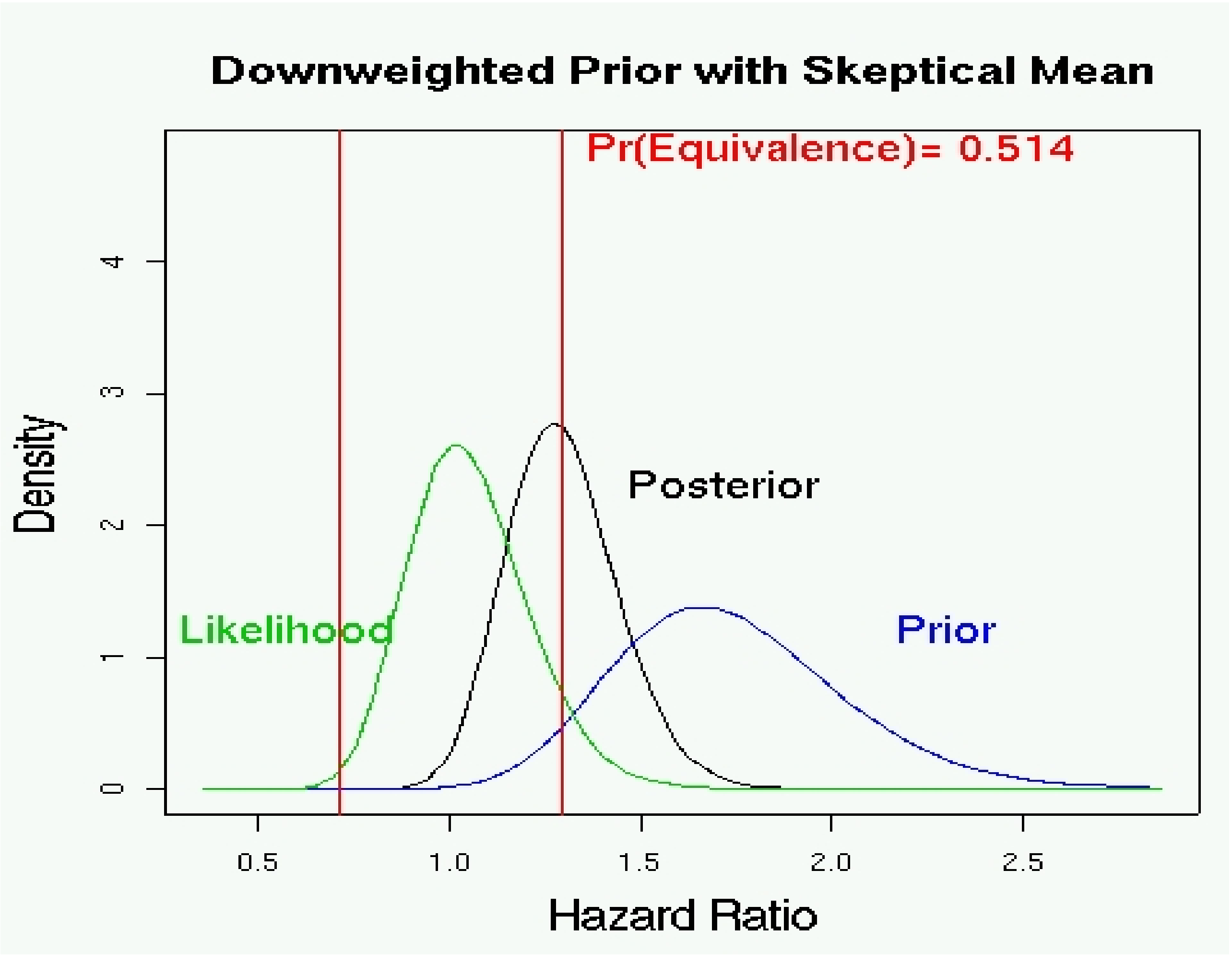
Case Study

New Study: GBS Study Group, *Lancet*, 1997

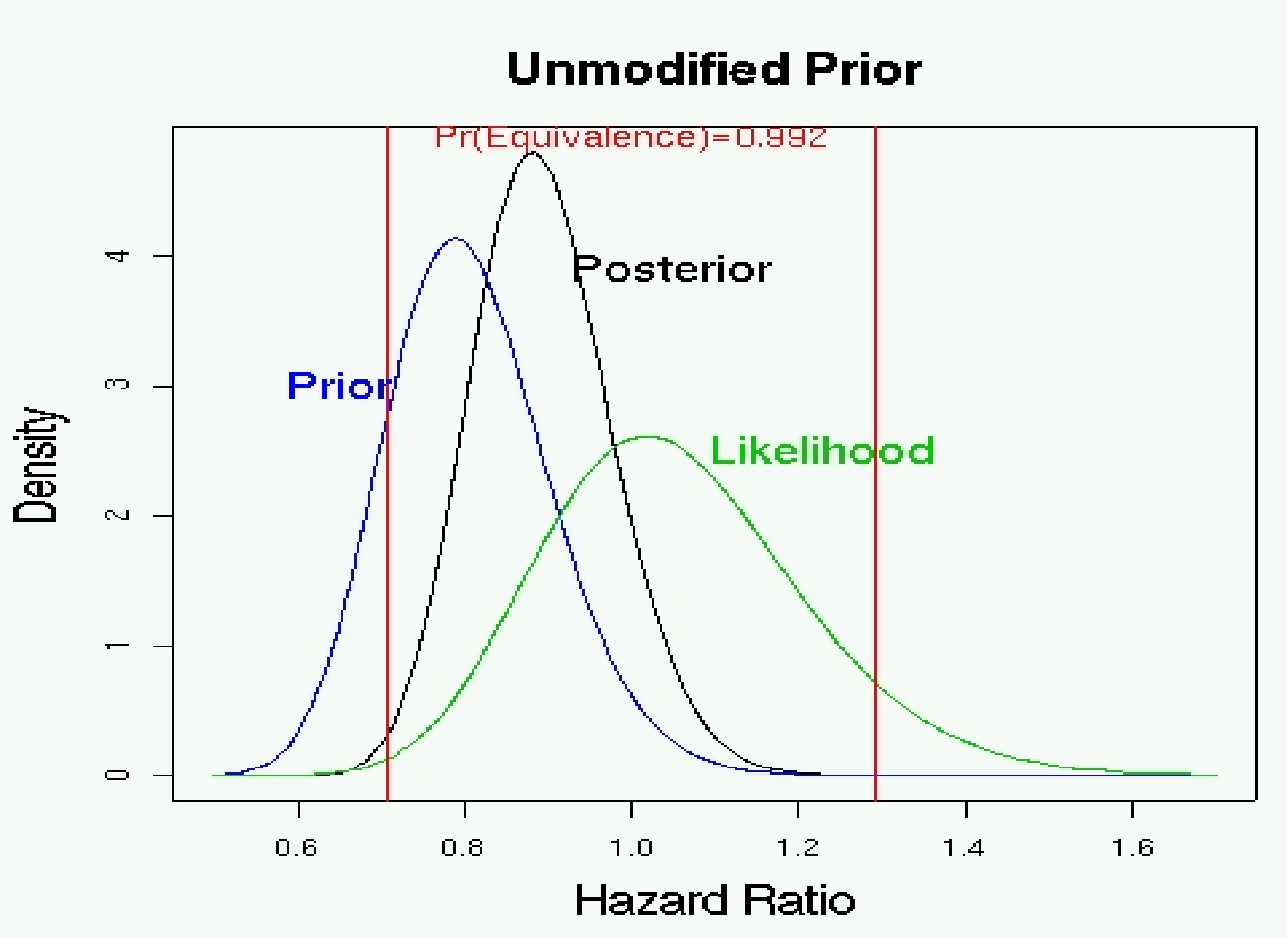
Treatment	Median Time to Walking (days)	Sample Size
IVIg	51 days	N = 127
PE	49 days	N= 114
Hazard Ratio (HR)	**51/49 = 1.04** (CI: 0.80 – 1.4)	



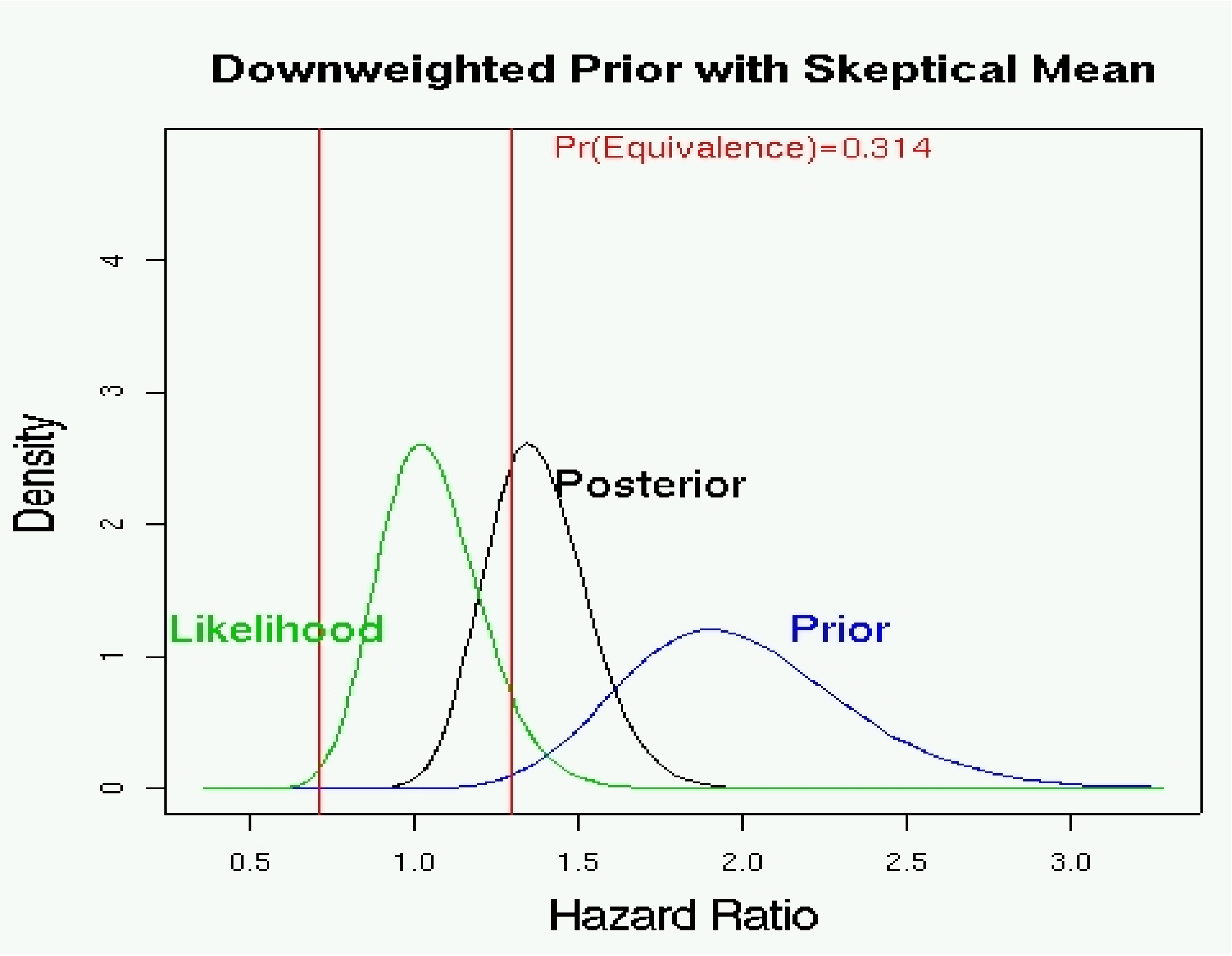
Downweighted Prior
Pr(Equivalence)=0.99
Posterior
Likelihood
Prior
Density
0
1
2
3
4
0.6
0.8
1.0
1.2
1.4
1.6
Hazard Ratio



Downweighted Prior with Skeptical Mean
Pr(Equivalence)= 0.514
Posterior
Likelihood
Prior
Density
Hazard Ratio
0
1
2
3
4
0.5
1.0
1.5
2.0
2.5



Unmodified Prior
Pr(Equivalence)=0.992
Posterior
Prior
Likelihood
Density
Hazard Ratio
0
1
2
3
4
0.6
0.8
1.0
1.2
1.4
1.6


Downweighted Prior with Skeptical Mean
Pr(Equivalence)=0.314
Posterior
Likelihood
Prior
Density
Hazard Ratio
0
1
2
3
4
0.5
1.0
1.5
2.0
2.5
3.0