abbvie

When to alert a Safety Assessment Committee – A Bayesian Approach with Example

ASA Biopharm Safety Monitoring Working Group Session
Joint Statistical Meeting, Baltimore, MD

Brian Waterhouse

02August2017

Disclaimer

The support of this presentation was provided by AbbVie. AbbVie participated in the review and approval of the content.

Brian Waterhouse is an employee of AbbVie, Inc.

Preliminary Summary

The FDA Draft Guidance on Safety Assessment for IND Safety Reporting introduced the concept of an unblinded Safety Assessment Committee

In order to maintain study integrity while still benefiting from the project team's expertise, blinded methodologies of safety signal detection are needed.

BDRIBS is a novel Bayesian methodology that allows the exploration of safety events in terms of relative risk to a control whose historical event rate has been previously investigated.

Contour plots and interactive graphics can help teams further explore assumptions before deciding whether an unblinded assessment is required.

Safety Assessment for IND Safety Reporting: Draft Guidance for Industry (December 2015)

FDA recommends that sponsors develop a Safety Assessment Committee (SAC) and a Safety Surveillance Plan (SSP) as "key elements of a systematic approach to safety surveillance"

"The safety assessment committee should oversee the evolving safety profile of the investigational drug by evaluating, at appropriate intervals, the cumulative serious adverse events from all of the trials in the development program, as well as other available important safety information (e.g., findings from epidemiological studies and from animal or in vitro testing) and performing ***unblinded*** comparisons of event rates in investigational and control groups, as needed" (Lines 188-192)

AbbVie instituted a pilot program to look to operationalize these recommendations:

1. SAC – consists of a team of internal experts that may become unblinded and will then determine whether an AE meets the criteria for IND safety reporting
2. Product safety teams look at blinded data – alert SAC if unblinding needed for specific AEs

Philosophy

Blinded safety monitoring is a complex endeavor that requires a ***multi-disciplinary*** approach to ensure that appropriate steps are taken in the event that a possible safety signal has been identified.

We are focused on the identification of possible safety signals based on relative risk and have developed a methodology and an interactive graphics tool to help safety teams investigate the magnitude of risk of a given event type.

What this method does:

1. Provides a quantitative framework for teams to discuss the potential risk based on the prior historical event rate and blinded observed events
2. Allows teams to investigate various levels of relative risks (RR) – providing flexibility to look at multiple scenarios
3. For relative risks of concern, provides a framework to help teams identify when a closer look is warranted
4. Allows easy exploration of the sensitivity of the signal under various assumptions.

BDRIBS

1. BDRIBS (Bayesian Detection of Risk using Inference on Blinded Safety data) is a Bayesian methodology developed at AbbVie
2. Key statistical concepts:
   - The method models Relative Risk (r) of an investigational drug (1) versus control (0) and considers a single event category (e.g. All Malignancies excluding NMSC)
   - Assume that events follow a Poisson process

$$Y_j \sim Poisson(\lambda_j), j = 0,1$$

where $\lambda_j = \delta_j * E_j$ (δ_j = true incidence rate, E_j = patient-years at risk)

- Note 1: the sum of independent Poisson RVs is also Poisson, so the total number of events Y is Poisson
- Note 2: the conditional Poisson is a Binomial, we can have:

$$Y_1 | \, Y \sim Bin(Y, p)$$

where, $p = \frac{\delta_1}{\delta_0 + \delta_1}$ (in the 1:1 randomization case)

- Note 3: $r = \delta_1/\delta_0$ and therefore $p = r/(1+r)$
- From notes 1-3 we can induce a prior distribution on r from a prior distribution on p
- This prior *plus* blinded observed data from ongoing trials yields a posterior distribution on r
- Since the posterior distribution is not of standard form, we need to use MCMC simulations to generate samples from the posterior distribution.

An example

We know from a large epidemiology study* that the rate of Malignancy excluding NMSC in rheumatoid arthritis (RA) is 0.85 events per 100 patient years. 95% CI: 0.70 to 1.02

Suppose that we are conducting a series of phase 3 trials in RA. The designs of the trials are such that the overall randomization ratio of 2:1 and the overall exposure of these trials is expected to be 1000 patient years.

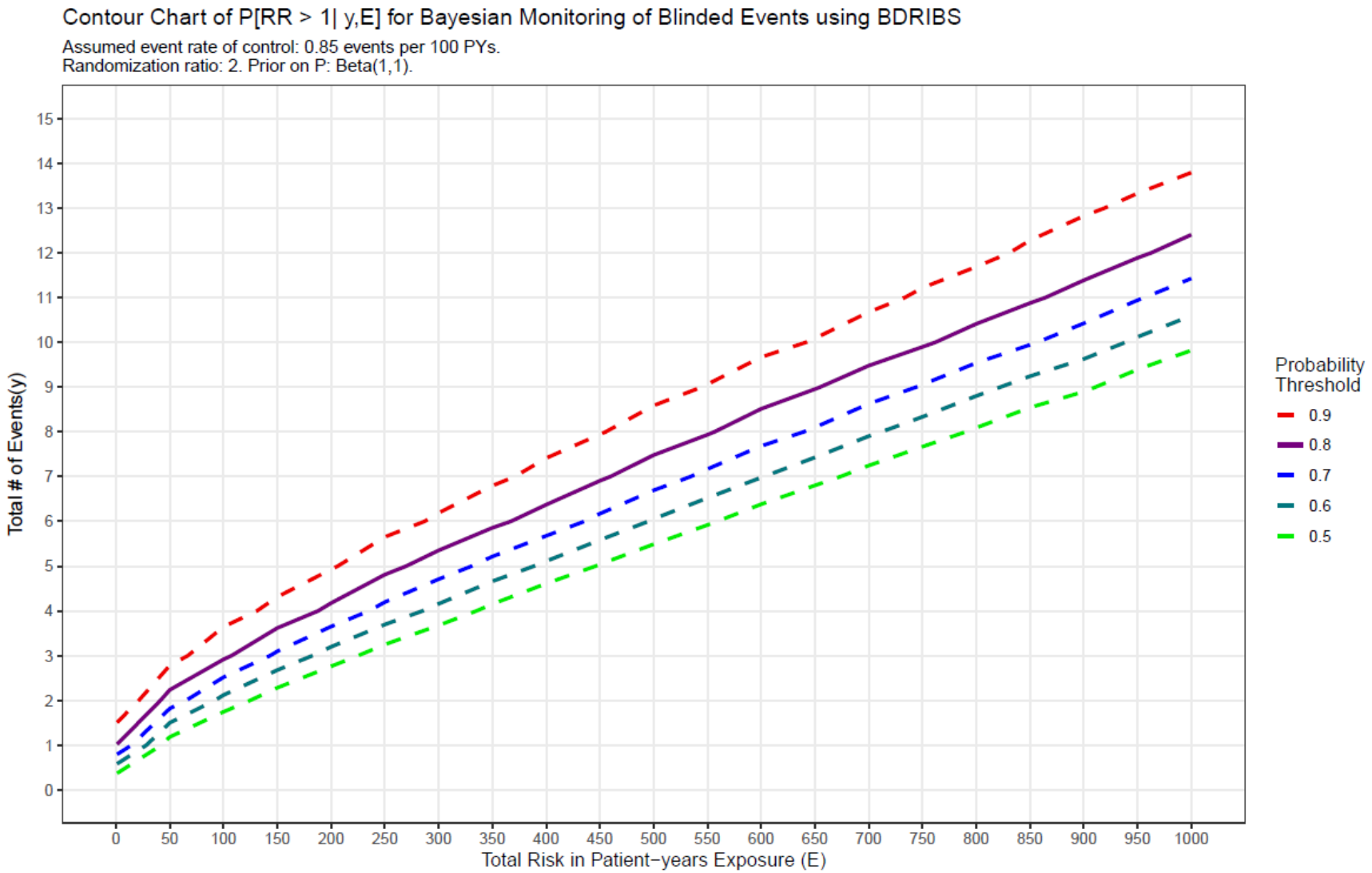
Furthermore assume a non-informative prior on the relative risk and that the team has made the following determination (a priori):

1. Relative Risk = 1 is of interest
2. If the probability that the RR > 1 | observed data is greater than 80%, a closer look is warranted.

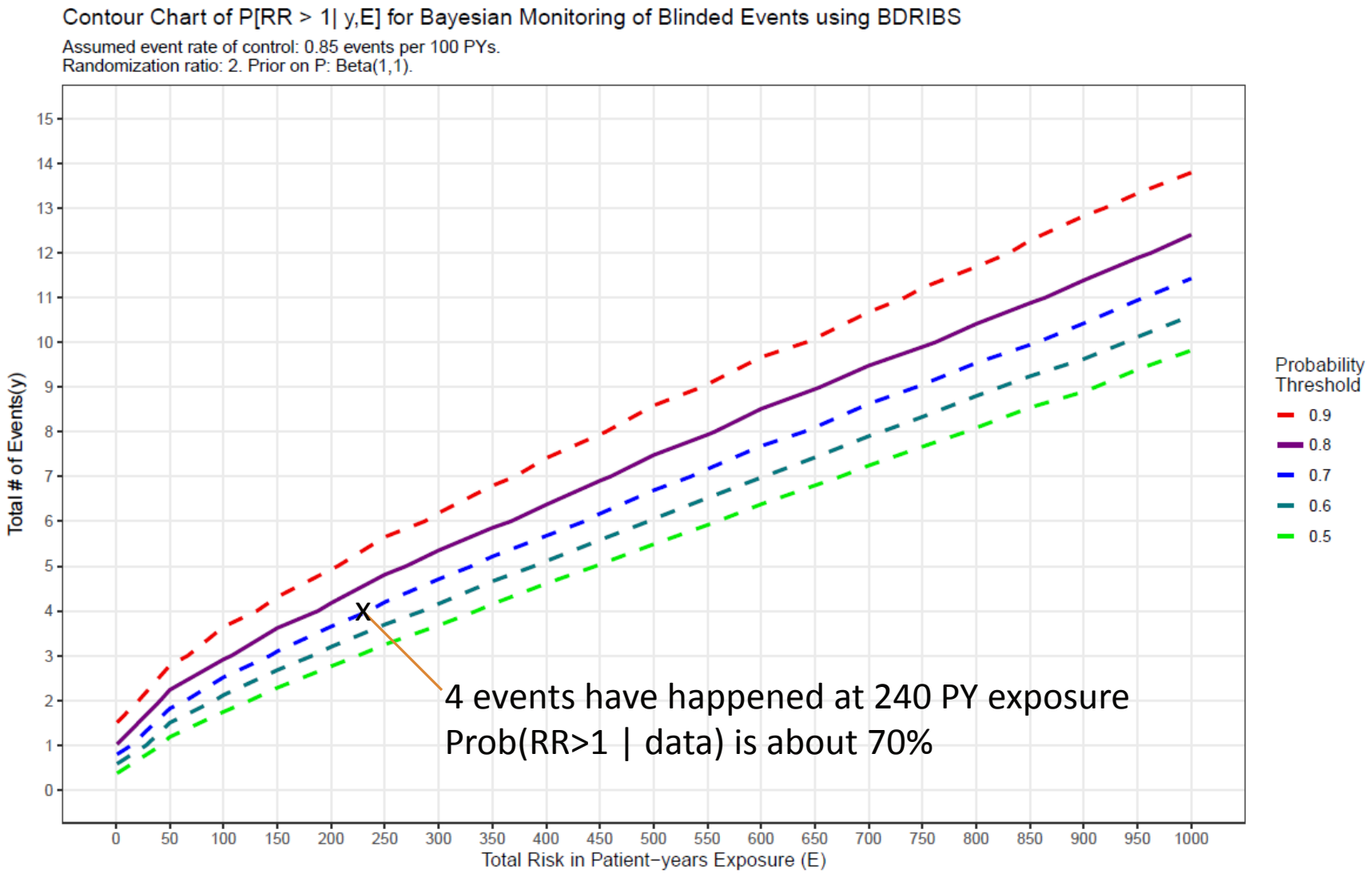
These details (1. & 2.) are included in the SSP.

* Curtis JR, Lee EB, Kaplan IV, et al. Ann Rheum Dis 2016;75:831–841.

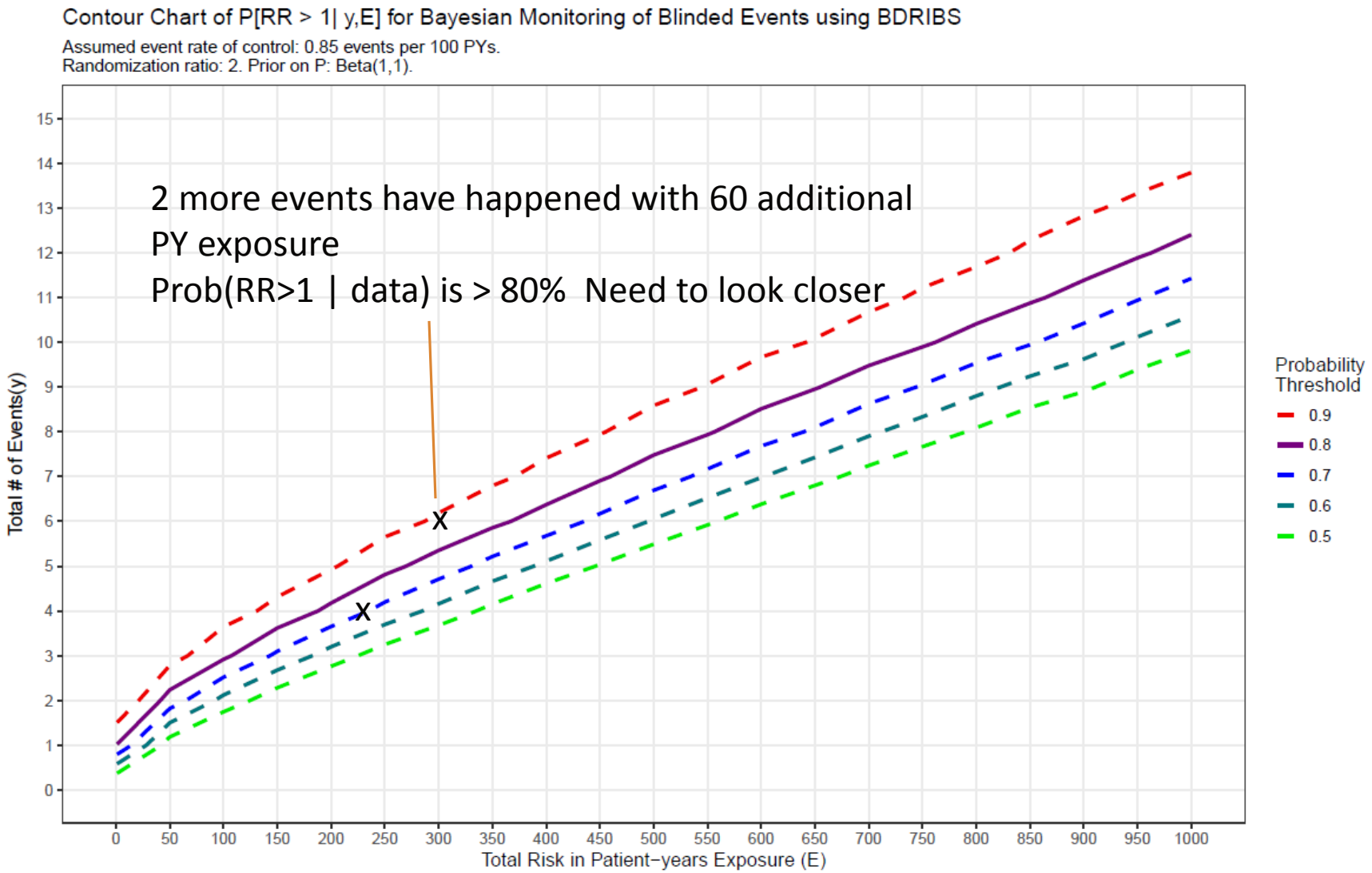
A contour plot can be generated prior to the trial...



A contour plot can be generated prior to the trial...



A contour plot can be generated prior to the trial...



Shiny BDRIBS

An interactive graphics tool has been developed to assist the team in their investigations.

Questions the methodology can help with:

1. How do changes in our assumption of control rate impact the probability?
2. How much additional exposure must accrue without an event in order for the probability to become acceptable?
3. At what RR cut-point does the probability RR > cut-point become acceptable?

Team discussion is needed to determine what is acceptable in terms of

- RR cut-point (e.g. c=1.2 if 20% increase is clinically meaningful, but <20% increase is not considered to be of concern)
- Probability threshold – Bayes factor and Jeffrey's scale may help the team decide on an appropriate threshold

Investigations

Safety Signal Exploration using BDRIBS

Prior assumptions:

- (•) Delta0 is fixed (Validated)
- ( ) Delta0 ~ Gamma

Randomization Ratio (Active/Control)

2

Prior Alpha for P

1

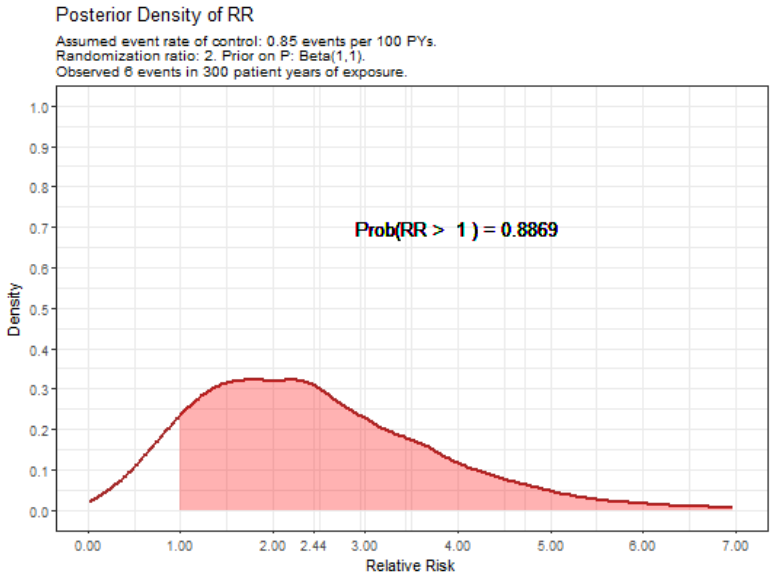
Prior Beta for P

1

Historical rate to compare in events per 100 PYs

0.85

Instructions | Posterior Bayesian Inference Plot | Contour Plot | Prior Plots



Number of Events Observed (Blinded)

1 | 6 | 25

1 4 7 10 13 16 19 22 25

Blinded Patient Years Exposure

40 | 300 | 2,000

40 240 440 640 840 1,240 1,640 2,000

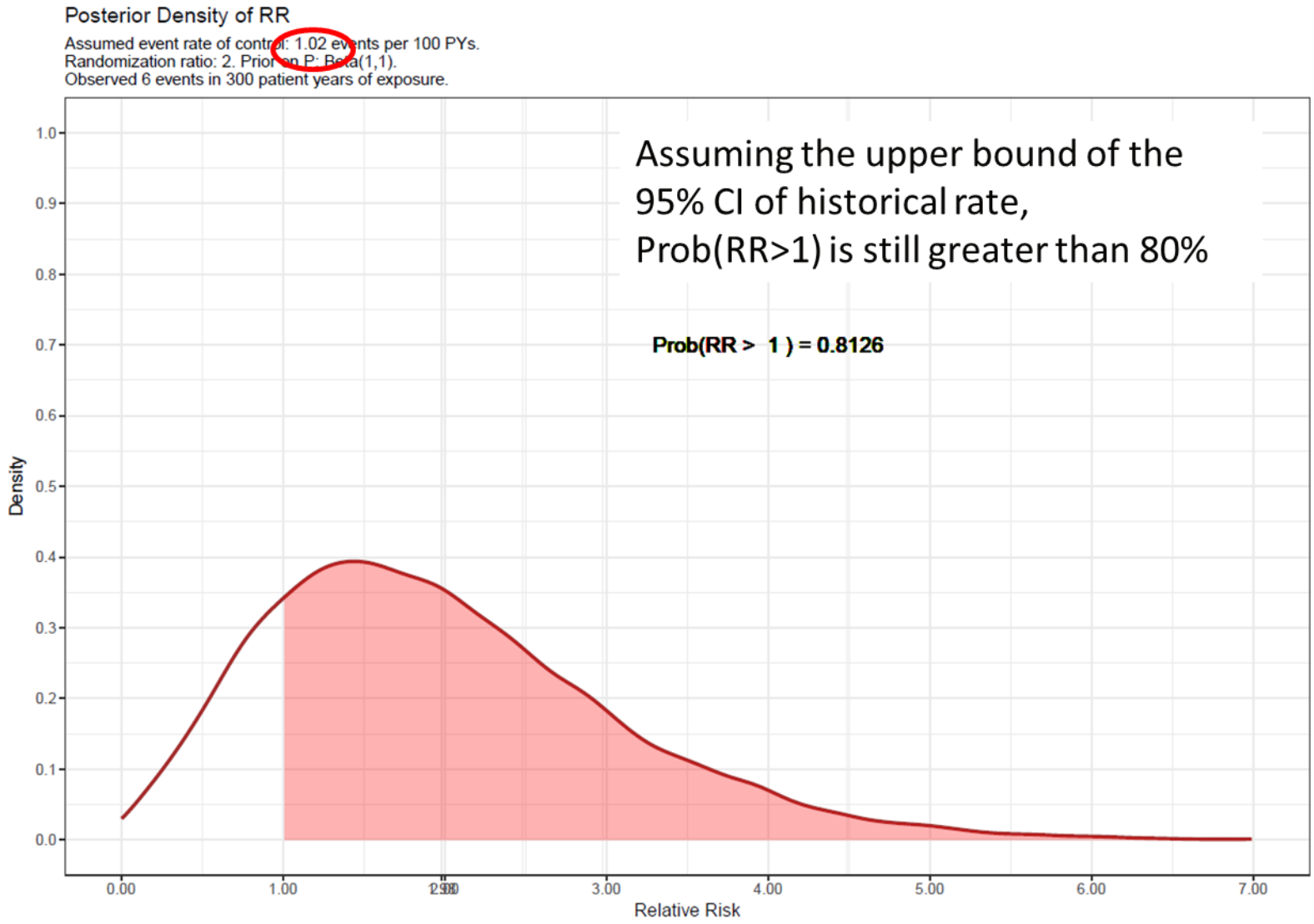
RR Cut-point values

0 | 1 | 5

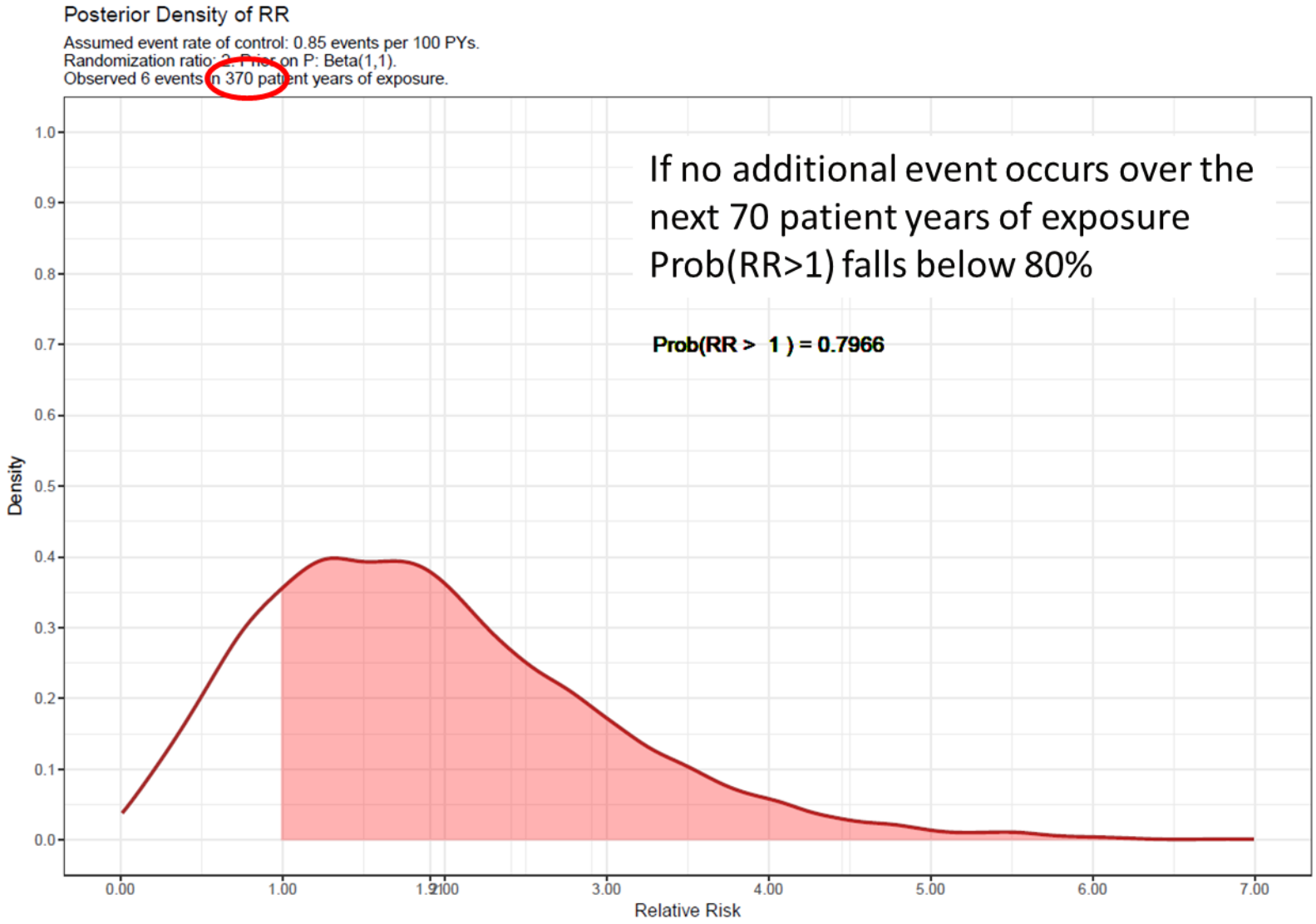
0 0.5 1 1.5 2 2.5 3 3.5 4 4.5 5

Bayesian Inference Plot

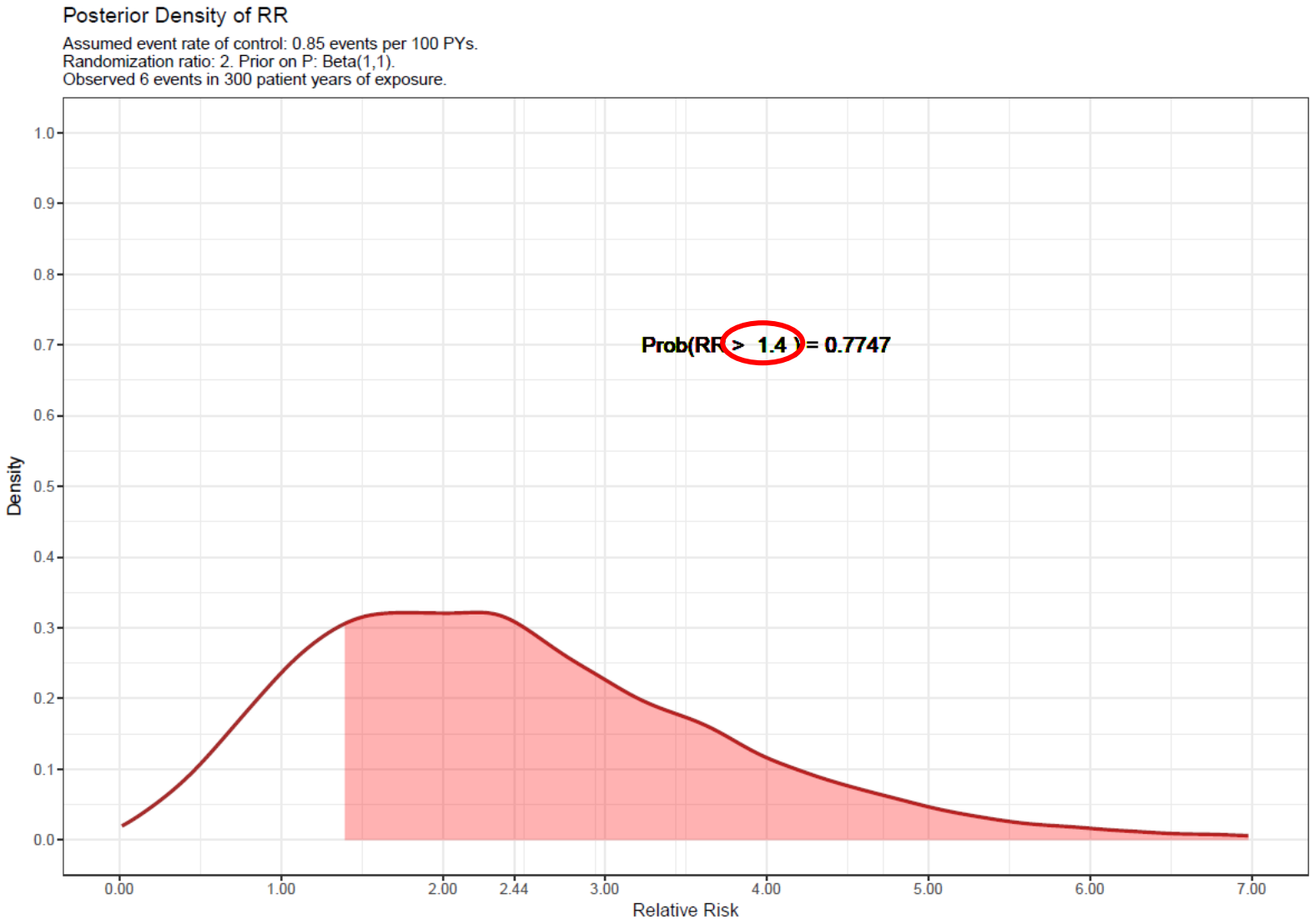
Changing assumptions on control rate



Additional exposure



Relative Risk Investigations



Concluding Remarks

The FDA Draft Guidance on Safety Assessment for IND Safety Reporting introduced the concept of an unblinded Safety Assessment Committee

In order to maintain study integrity while still benefiting from the project team's expertise, blinded methodologies of safety signal detection are needed.

BDRIBS is a novel Bayesian methodology that allows the exploration of safety events in terms of relative risk to a control whose historical event rate has been previously investigated.

Contour plots and interactive graphics can help teams further explore assumptions before deciding whether an unblinded assessment is required.

Acknowledgements

Saurabh Mukhopadhyay – lead developer of the statistical methodology

Walt Offen and Alan Hartford for additional statistical input and advice.

Ping Jiang, Ranjeeta Sinvhal, Barbara Hendrickson, Syed Islam and other members of the pilot team for many discussions on the method and implementation.

abbvie

Back-ups

Bayesian Hypothesis Testing of Signal Strength

- In Bayesian inference, the use of Bayes Factors (BF) is a Bayesian alternative to classical hypothesis testing (see e.g., Berger, 1985; Kass and Raftery, 1995; Goodman, 1999).
- Bayes Factor of H_1 to H_0 is defined as the ratio of marginal likelihoods (to test say, $H_0 : r \leq c \; vs. H_1 : r > c$)
- It is often easier to compute the prior and posterior odds and use the expression to compute the BF:

$$\frac{P(H_1|x)}{P(H_0|x)} = \frac{P(H_1)}{P(H_0)} * BF$$

(posterior odds) (prior odds) (Bayes Factor)

Bayes Factor (cont.)

- A value of BF > 1 means that data supports H_1 more than H_0.
- There are limits on changes in a weight of evidence (i.e. a change in an odds ratio, or BF) that humans can reasonably perceive their degree of belief in a hypothesis in everyday use (Good, 1979).
- Scales are suggested by Jeffrey (1961) to interpret the BF:

BF	Strength of Evidence in favor of H_1
<1	Negative (supports H_0)
1 to 3	Barely worth mentioning
3 to 10	Substantial
10 to 30	Strong
30 to 100	Very strong
> 100	Decisive

Note: There is another slightly different scale suggested by Kass and Raftery (1995).

Contact information: brian.waterhouse@abbvie.com