Bayesian approaches in clinical trials

André Moser, CTU Bern, University of Bern

17/04/2023

Table of contents

1 Introduction

1.1 General notation and abbreviations

- iid: independent and identically distributed
- pdf: probability density function
- N_2: Bivariate cumulative Gaussian distribution function
- ϕ: Probability density function of the standard Gaussian distribution
- Φ: Cumulative distribution function of the standard Gaussian distribution
- Φ^{-1}: Quantile function of the standard Gaussian distribution function

1.2 'Power' vocabulary

In their supplement Kunzmann et al. [1] provide a literature review of the terminology used in articles. We provide here a summary of this terminology:

- **Frequentist power**: Probability of rejection given that the alternative hypothesis is true.
- **Average power**: Prior averaged probability of rejection. Often also called 'probability of success', 'assurance', 'Bayesian predictive power'.
- **Prior adjusted power**: Joint probability of rejection and that the treatment effect is effective.

1.3 Some 'Bayesian' concepts

- **Design prior**: Priors used before data collection as data generating mode [2].
- **Analysis prior**: Priors used for Bayesian analysis of the collected data [2].

3

- **Prior predictive distribution**: Situation *before* a sample was taken. Let θ be a realisation of a random variable Θ with pdf $p(\theta)$. Then for a future observation $\tilde{X}$

$$p(\tilde{x}) = \int_\Theta p(\tilde{x}, \theta) d\theta = \int_\Theta \underbrace{p(\tilde{x}|\theta)}_{likelihood} \underbrace{p(\theta)}_{prior} d\theta$$

- **Posterior predictive distribution**: Situation *after* a sample was taken. Let θ be a realisation of a random variable Θ with pdf $p(\theta)$. Then for a future observation $\tilde{X}$ and observed X (since X is independent $\tilde{X}$)

$$p(\tilde{x}|x) = \int_\Theta p(\tilde{x}|\theta, x) p(\theta|x) d\theta = \int_\Theta \underbrace{p(\tilde{x}|\theta)}_{likelihood} \underbrace{p(\theta|x)}_{prior} d\theta.$$

1.4 Used R libraries

```
library(tidyverse)
library(epiR)
library(mvtnorm)
library(extraDistr)
library(PropCIs)
```

2 Power and sample size calculations

2.1 Background

The terminology of 'power' is often imprecisely used [1]. Kunzmann et al. suggest to use the neutral term 'probability to reject'. The classical (frequentist) 'power' is defined as the probability to reject given that the alternative hypothesis is true. Frequentist power calculations do not include uncertainties of the treatment effect, whereas Bayesian and hybrid approaches include such uncertainties in their calculations. In the following we use different approaches for the calculation of the 'probability to reject' (frequentist, Bayesian and hybrid) for different clinical trial designs.

Definition 'hybrid' ([3], Section 6.5.2)

'[...] we have a prior distribution to use in our study design, but that the conclusions of the study will be entirely classical and will not make use of the prior [...]'

2.2 Two-arm non-inferiority setting

In this section we consider a non-inferiority clinical trial setting with a null hypothesis $H_0 : \delta > \delta^*$ and alternative hypothesis $H_a : \delta \leq \delta^*$, where $\delta^* > 0$ is a fixed non-inferiority margin and a treatment effect δ, for example, a continuous difference or a risk difference.

Treatment effect (<−−− favors active treatment)
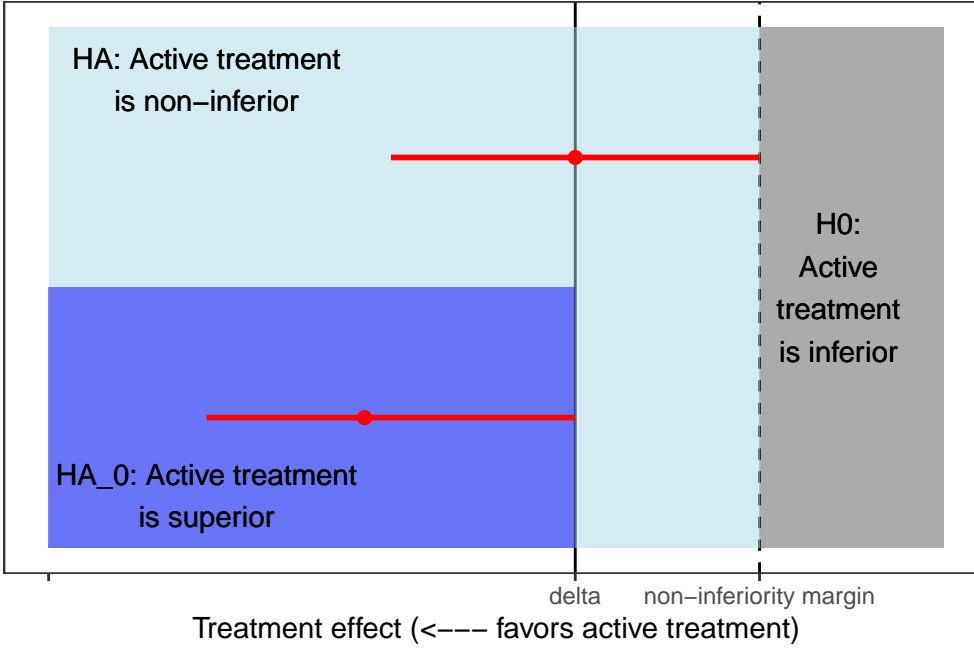
2.2.1 Binomial outcome

Here p_1 and p_0 are event probabilities from an active treatment arm and a control arm, respectively. $\delta = p_1 - p_0$ is the true treatment effect expressed as a risk difference.

In this section we assume that the variances in both groups are known, but might be different.

Working example

We use the SAFE-SSPE trial as a working example [4]. In brief, this non-inferiority randomised placebo-controlled trial compares clinical surveillance versus anticoagulant treatment in low-risk patients with isolated subsegmental pulmonary embolism (SSPE). The primary outcome is the proportion of 3-month recurrence of venous thromboembolism (VTE).

The null hypothesis H_0 is *'clinical surveillance is inferior to anticoagulant treatment'* versus the alternative hypothesis H_a *'clinical surveillance is non-inferior to anticoagulant treatment'*. Thus, $H_0 : p_1 - p_0 > 0$

vs $H_a : p_1 - p_0 \leq 0$, where p_1 is the VTE proportion in the clinical surveillance arm and p_0 is the VTE proportion in the control arm.

The non-inferiority margin was set at 3.5% and it was assumed that the proportion of VTE in both groups was 1%.

2.2.1.1 Frequentist approach

Let $Y_{i,k} \sim^{iid} Bernoulli(p_i)$, $k = 1, \ldots, n_i$, $i \in \{0, 1\}$. Let $\bar{p}_i = \frac{1}{n_i} \sum_{k \leq n_i} Y_{i,k}$, $i \in 0, 1$, and thus the estimated risk difference $D = \bar{p}_1 - \bar{p}_0$ is asymptotically Gaussian distributed with $D \sim N\left(\delta, \frac{\sigma_1^2}{n_1} + \frac{\sigma_0^2}{n_0}\right)$, where $\sigma_i^2 = p_i(1 - p_i)$, $i \in \{0, 1\}$. For notational purposes we denote $\sigma_{treat}^2 = \frac{\sigma_1^2}{n_1} + \frac{\sigma_0^2}{n_0}$, that is, the variance for the treatment effect.

We are interested whether the upper $(1 - \alpha)\%$-confidence limit is smaller than the non-inferiority margin, that is,

$$D + z_{1-\alpha}\sqrt{\frac{n_0\sigma_1^2 + n_1\sigma_0^2}{n_1 n_0}} \leq \delta^*,$$

where $z_{1-\alpha} = \Phi^{-1}(1 - \alpha)$. Simple algebra leads to

$$D \leq -z_{1-\alpha}\sqrt{\frac{n_0\sigma_1^2 + n_1\sigma_0^2}{n_1 n_0}} + \delta^*.$$

Note that $D_{suc}^{\delta^*} := -z_{1-\alpha}\sqrt{\frac{n_0\sigma_1^2 + n_1\sigma_0^2}{n_1 n_0}} + \delta^*$ is the **required risk difference** for a 'successful' rejection of the null hypothesis. Then

$$
\begin{aligned}
P_\delta(D \leq D_{suc}^{\delta^*}) &= \Phi\left(-z_{1-\alpha} - \sqrt{\frac{n_1 n_0}{n_0\sigma_1^2 + n_1\sigma_0^2}}(\delta - \delta^*)\right) \\
&= \Phi\left(-z_{1-\alpha} - \frac{(\delta - \delta^*)}{\sigma_{treat}}\right),
\end{aligned}
$$

since under regularity conditions,

$$Z = \frac{D - \delta^*}{\sigma_{treat}} \to N(0, 1), \quad \min(n_1, n_0) \to \infty.$$

The conditional probability $P_\delta(D \leq D_{suc}^{\delta^*})$ is the **probability to reject given** δ. For $\delta > \delta^*$ this is the 'type-I error' and for $\delta \leq \delta^*$ this is the frequentist 'power'.

For a δ_A it holds that

$$-z_{1-\alpha} - \sqrt{\frac{n_1 n_0}{n_0 \sigma_1^2 + n_1 \sigma_0^2}} (\delta_A - \delta^*) = \Phi^{-1}(1 - \beta) = z_{1-\beta}$$

and so the sample size can then be derived as

$$\frac{(z_{1-\beta} + z_{1-\alpha})^2}{(\delta_A - \delta^*)^2} = \frac{a n_0^2}{n_0 \sigma_1^2 + a n_0 \sigma_0^2},$$

where $a = n_1/n_0$ is an allocation ratio, such that

$$n_0 = (z_{1-\beta} + z_{1-\alpha})^2 \frac{\sigma_1^2 + a \sigma_0^2}{a(\delta_A - \delta^*)^2}, \quad n_1 = a n_0.$$

δ_0, δ_A and δ^* are assumed as fixed and known constants in a frequentist approach. Their choices are of high importance, because all trial conclusions are based on those choices and affect the sample size calculation. The plot below shows how the sample size increase as δ^* approaches δ.
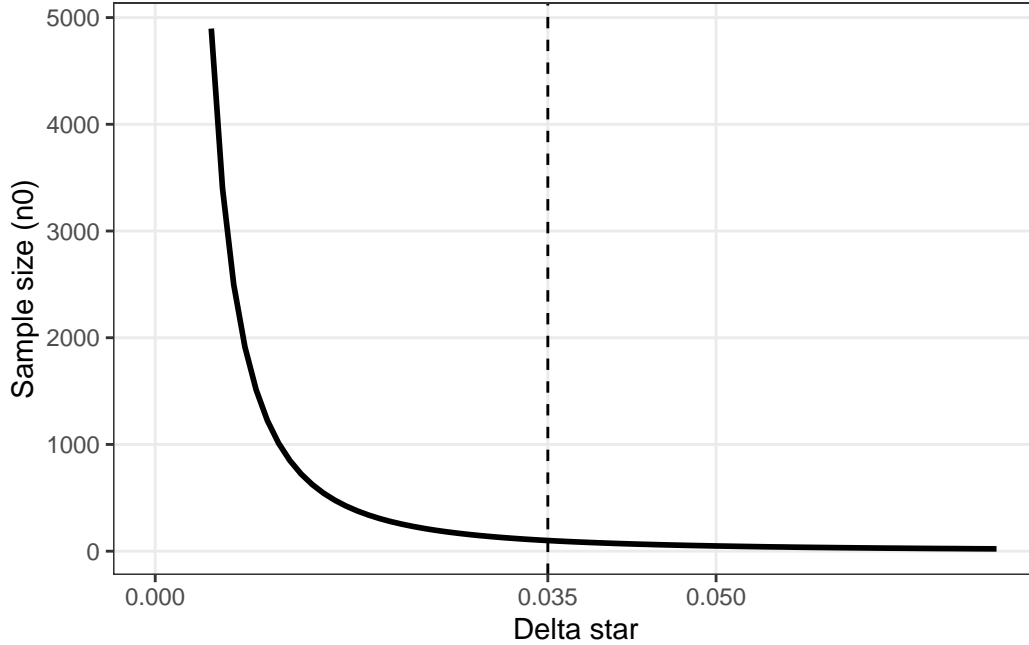
Working example (continued)

We calculate the required sample size for the SAFE-SSPE trial using a frequentist approach with the following parameters:

- $p_1 = 0.01$, $p_0 = 0.01$, $\delta^* = 0.035$, $1 - \beta = 0.8$, $\alpha = 0.05$, $a = 1/1$

```r
library(epiR)

alpha <- 0.05
beta <- 0.2
p_0 <- 0.01
p_1 <- 0.01
delta <- p_1 - p_0
delta_star <- 0.035
sd_0 <- sqrt(p_0 * (1 - p_0))
sd_1 <- sqrt(p_1 * (1 - p_1))
a <- 1/1

epi.ssninfb(treat = p_1, control = p_0, delta = delta_star, power = 1 -
    beta, r = a, alpha = alpha, n = NA)
```

```
$n.total
[1] 200


$n.treat
[1] 100


$n.control
[1] 100
```

```
$delta
[1] 0.035


$power
[1] 0.8
```

```
  n_0 <- ((qnorm(1 - beta) + qnorm(1 - alpha))^2) * ((sd_1^2 +
      a * sd_0^2)/(a * (delta - delta_star)^2))
  n_0
```

```
[1] 99.93031
```

```
  n_1 <- n_0 * a
  n_1
```

```
[1] 99.93031
```

Under the specified parameters a sample size of 200 patients (100 per arm) is needed to reject the null hypothesis of inferiority. This is more or less the sample size mentioned in the study protocol of the SAFE-SSPE trial but without dropouts and adjustments for rare events.

2.2.1.2 Hybrid approach: Prior on the treatment effect

Suppose that the true treatment effect δ is a realization from a random variable Δ with $p(\delta)$. In this subsection we assume that the design prior comes from a Gaussian distribution function so that $\Delta \sim N\left(d, \frac{\sigma_1^2 + \sigma_0^2}{m}\right)$. Note that this prior can be thought as a realisation from m Gaussian 'prior observations' with variance $\sigma_1^2 + \sigma_0^2$. Again for notational purposes we denote $\sigma_{prior}^2 = \frac{\sigma_1^2 + \sigma_0^2}{m}$ as the variance of the design prior on the treatment effect.

In the following we will use the following design priors:

- **Enthusiastic prior** (favors non-inferiority): $d = 0$, $m = 6.6$, $P(\Delta > \delta^*) = 0.05$. This prior is centered on the treatment effect such that there is a low probability (here 5%) of inferiority.

- **Skeptical prior** (favors inferiority): $d = \delta^*$, $m = 6.6$, $P(\Delta > 0) = 0.05$. This prior is centered on the non-inferiority margin such that there is a low probability (here 5%) of superiority.

- **Informative prior** (clinical expert knowledge): $d = 0$ with $m = 25$.

- **Noninformative prior**: $d = 0$ with $m = 0.5$.
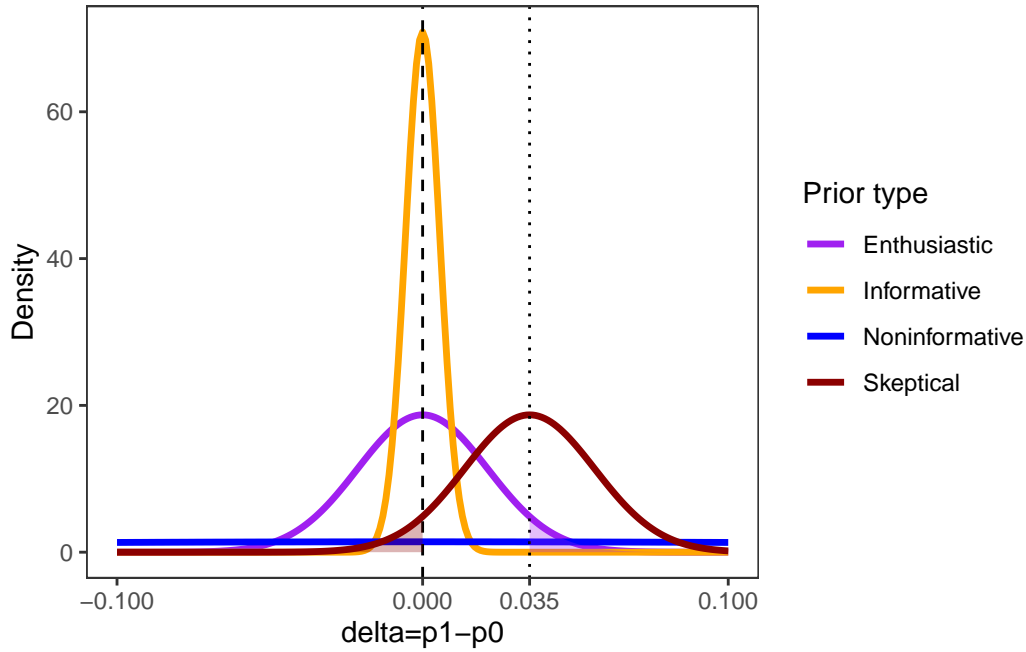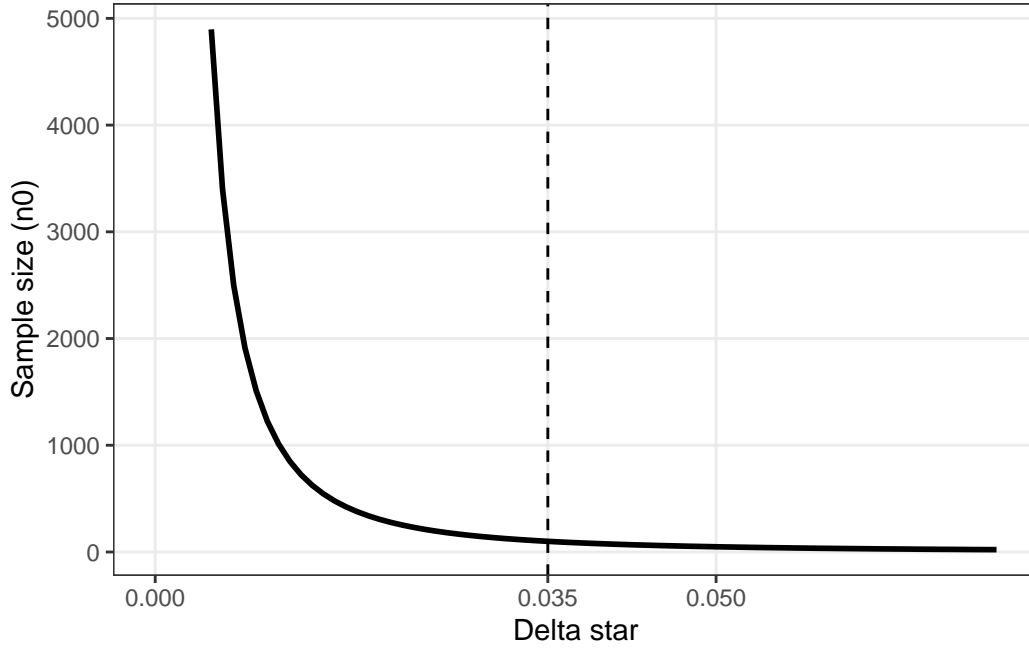
Let

$$AP := \int_{\Delta} P_{\delta}(D \le D_{suc}^{\delta^*})p(\delta)d\delta,$$

be the **'average power'** [5] (also called 'assurance' [6], 'probability of success' [1], [3] or Bayesian predictive power [7]. The supplemental section of [1] contains a literature review of the used terminology). Remember that in an hybrid approach we are interested in trial conclusions from a frequentist point of view, thus we are interested in

$$D \le -z_{1-\alpha}\sqrt{\frac{n_0\sigma_1^2 + n_1\sigma_0^2}{n_1 n_0}} + \delta^*.$$

By using a design prior we take into account the uncertainty of the treatment effect. The prior predictive distribution for an estimated risk difference, say $\tilde{D}$, with a prior $\Delta \sim N\left(d, \sigma_{prior}^2\right)$ includes this uncertainty. For the Gaussian case, the prior predictive distribution of $\tilde{D}$ is given as

$$\tilde{D} \sim N\left(d, \sigma_{treat}^2 + \sigma_{prior}^2\right),$$

since $\tilde{D} \sim N\left(\delta, \sigma_{treat}^2\right)$.

Suppose now that D has a predictive distribution as described above, then

$$AP = \int_{-\infty}^{-z_{1-\alpha}\sqrt{\frac{n_0\sigma_1^2+n_1\sigma_0^2}{n_1 n_0}}+\delta^*} f(\tilde{\delta})d\tilde{\delta} = \Phi\left(\frac{1}{\sigma_{prior}}\left[-z_{1-\alpha}\sigma_{treat} - (d - \delta^*)\right]\right)$$

see for example [5]. Note that as $m \to \infty$, then $AP \to \Phi\left(-z_{1-\alpha} - \frac{(d-\delta^*)}{\sigma_{treat}}\right)$, that is, the frequentist power at d.

Working example (continued)

We calculate the AP under the assumed prior distributions and parameters for the SAFE-SSPE trial.

```r
# Enthusiastic prior
m <- 6.6
prior_mean <- 0
sigma_prior <- sqrt((sd_0^2 + sd_1^2))/sqrt(m)
sigma_treat <- sqrt((sd_0^2/n_0 + sd_1^2/n_1))


AP <- pnorm(1/sigma_prior * (-qnorm(1 - alpha) * sigma_treat -
    (prior_mean - delta_star)))


data_output <- data.frame(type = "Enthusiastic", n_0, n_1, AP = round(AP,
    2))


# Skeptical prior
m <- 6.6
prior_mean <- delta_star
sigma_prior <- sqrt((sd_0^2 + sd_1^2))/sqrt(m)
sigma_treat <- sqrt((sd_0^2/n_0 + sd_1^2/n_1))


AP <- pnorm(1/sigma_prior * (-qnorm(1 - alpha) * sigma_treat -
```

```r
        (prior_mean - delta_star)))

data_output <- rbind(data_output, data.frame(type = "Skeptical",
    n_0, n_1, AP = round(AP, 2)))


# Informative prior
m <- 25
prior_mean <- 0
sigma_prior <- sqrt((sd_0^2 + sd_1^2))/sqrt(m)
sigma_treat <- sqrt((sd_0^2/n_0 + sd_1^2/n_1))


AP <- pnorm(1/sigma_prior * (-qnorm(1 - alpha) * sigma_treat -
    (prior_mean - delta_star)))


data_output <- rbind(data_output, data.frame(type = "Informative",
    n_0, n_1, AP = round(AP, 2)))


# Noninformative prior
m <- 0.5
prior_mean <- 0
sigma_prior <- sqrt((sd_0^2 + sd_1^2))/sqrt(m)
sigma_treat <- sqrt((sd_0^2/n_0 + sd_1^2/n_1))


AP <- pnorm(1/sigma_prior * (-qnorm(1 - alpha) * sigma_treat -
    (prior_mean - delta_star)))


data_output <- rbind(data_output, data.frame(type = "Noninformative",
    n_0, n_1, AP = round(AP, 2)))


data.frame(data_output %>%
```

```
             type        n_0       n_1    AP
1    Enthusiastic 99.93031 99.93031 0.59
2     Informative 99.93031 99.93031 0.66
3 Noninformative 99.93031 99.93031 0.52
4       Skeptical 99.93031 99.93031 0.34
```

Under an 'enthusiastic prior' we get an average power of 59%. For an 'skeptical prior' the average power decreases to 34%. These values are lower than the frequentist power of 80%.

Rufibach et al. give a closed a formula for the distribution of $RPR := P_\Delta(D \leq D_{suc}^{\delta^*})$, where $\Delta \sim N(d, \sigma_{prior}^2)$, and discuss the shape under different prior choices [7]. In the following we use the wording 'random probability to reject' (RPR) similar to [1].

For $0 < y < 1$, the random variable RPR has a probability density function

$$f(y) = \frac{\sigma_{treat}}{\sigma_{prior}} \phi \left(-z_{1-\alpha} \frac{\sigma_{treat}}{\sigma_{prior}} - \frac{(d - \delta^*)}{\sigma_{prior}} - \frac{\sigma_{treat}}{\sigma_{prior}} \Phi^{-1}(y) \right) \left[\phi \left(\Phi^{-1}(y) \right) \right]^{-1},$$

see [7].

Special case

For the case that $n_0 = n_1 = n$ and $\sigma_1^2 = \sigma_0^2 = \sigma^2$, then $\sigma_{treat}^2 = \frac{2\sigma^2}{n}$ and $\sigma_{prior}^2 = \frac{2\sigma^2}{m}$, and the formula above reduces to

$$f(y) = \sqrt{\frac{m}{n}} \phi \left(\sqrt{\frac{m}{n}} \left[-z_{1-\alpha} - \sqrt{\frac{n}{2\sigma^2}} (d - \delta^*) - \Phi^{-1}(y) \right] \right) \left[\phi \left(\Phi^{-1}(y) \right) \right]^{-1}, \quad 0 < y < 1.$$

Working example (continued)

We derive the probability densities for the different assumed design priors for the SAFE-SSPE study.

```r
x <- seq(0.001, 0.999, 0.001)


# Enthusiastic prior

m <- 6.6

prior_mean <- 0

sigma_prior <- sqrt((sd_0^2 + sd_1^2))/sqrt(m)

sigma_treat <- sqrt((sd_0^2/n_0 + sd_1^2/n_1))


## Rufibach 2016: formula (4)

y <- sqrt(m * n_0 * sd_1^2 + m * n_1 * sd_0^2)/(sqrt(n_1 * n_0 *

    (sd_0^2 + sd_1^2))) * dnorm(-sqrt(m * n_0 * sd_1^2 + m *

    n_1 * sd_0^2)/(sqrt(n_1 * n_0 * (sd_0^2 + sd_1^2))) * qnorm(1 -

    alpha) - sqrt(m)/sqrt((sd_0^2 + sd_1^2)) * (prior_mean -

    delta_star) - sqrt(m * n_0 * sd_1^2 + m * n_1 * sd_0^2)/(sqrt(n_1 *

    n_0 * (sd_0^2 + sd_1^2))) * qnorm(x)) * (dnorm(qnorm(x)))^(-1)


data_power <- data.frame(x, y, type = "Enthusiastic")


# Skeptical prior

m <- 6.6

prior_mean <- delta_star

sigma_prior <- sqrt((sd_0^2 + sd_1^2))/sqrt(m)

sigma_treat <- sqrt((sd_0^2/n_0 + sd_1^2/n_1))


y <- sigma_treat/sigma_prior * dnorm(-qnorm(1 - alpha) * sigma_treat/sigma_prior -
```

```r
    (1/sigma_prior) * (prior_mean - delta_star) - (sigma_treat/sigma_prior) *

    qnorm(x)) * (dnorm(qnorm(x)))^(-1)


data_power <- rbind(data_power, data.frame(x, y, type = "Skeptical"))


# Informative prior
m <- 25
prior_mean <- 0
sigma_prior <- sqrt((sd_0^2 + sd_1^2))/sqrt(m)
sigma_treat <- sqrt((sd_0^2/n_0 + sd_1^2/n_1))


y <- sigma_treat/sigma_prior * dnorm(-qnorm(1 - alpha) * sigma_treat/sigma_prior -

    (1/sigma_prior) * (prior_mean - delta_star) - (sigma_treat/sigma_prior) *

    qnorm(x)) * (dnorm(qnorm(x)))^(-1)


data_power <- rbind(data_power, data.frame(x, y, type = "Informative"))


# Noninformative prior
m <- 0.5
prior_mean <- 0
sigma_prior <- sqrt((sd_0^2 + sd_1^2))/sqrt(m)
sigma_treat <- sqrt((sd_0^2/n_0 + sd_1^2/n_1))


y <- sigma_treat/sigma_prior * dnorm(-qnorm(1 - alpha) * sigma_treat/sigma_prior -

    (1/sigma_prior) * (prior_mean - delta_star) - (sigma_treat/sigma_prior) *

    qnorm(x)) * (dnorm(qnorm(x)))^(-1)


data_power <- rbind(data_power, data.frame(x, y, type = "Noninformative"))


data_output2 <- data_output %>%
```

```
    select(type, x = AP) %>%
    mutate(y = 0)


data_power$type <- factor(data_power$type, levels = c("Enthusiastic",
    "Skeptical", "Informative", "Noninformative"))


ggplot(data_power, aes(x, y, colour = type)) + geom_line(linewidth = 1) +
    geom_point(data = data_output2, aes(x = x, y = y, colour = type)) +
    scale_colour_manual("Prior type", values = c("purple", "orange",
        "blue", "darkred")) + theme_bw() + theme(panel.grid = element_blank()) +
    ylab("Density") + xlab("RPR") + ylim(c(0, 2)) + labs(caption = "Dots indicate the AP.")
```


Dots indicate the AP.
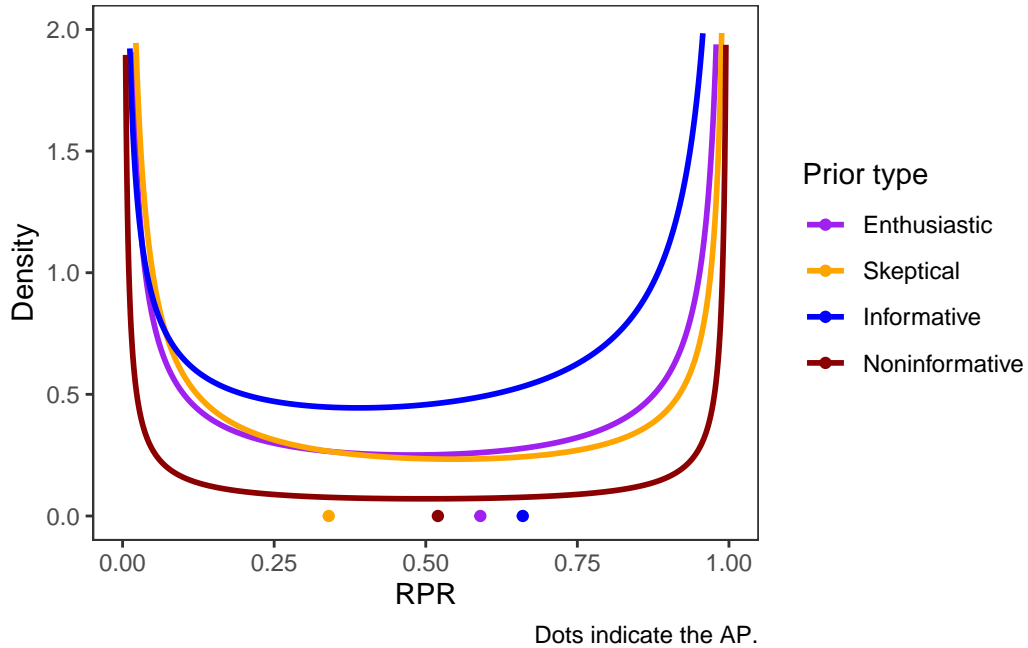
The cumulative distribution function of RPR can the be calculated as

$$P(RPR \leq y) = 1 - \Phi\left(\frac{\sigma_{treat}}{\sigma_{prior}}\left[-z_{1-\alpha} - \frac{(d - \delta^*)}{\sigma_{treat}} - \Phi^{-1}(y)\right]\right), \quad 0 < y < 1.$$

18

Special case

For the case that $n_0 = n_1 = n$ and $\sigma_1^2 = \sigma_0^2 = \sigma^2$, then $\sigma_{treat}^2 = \frac{2\sigma^2}{n}$ and $\sigma_{prior}^2 = \frac{2\sigma^2}{m}$, and the formula above reduces to

$$P(RPR \leq y) = 1 - \Phi\left(\frac{\sigma_{treat}}{\sigma_{prior}}\left[-z_{1-\alpha} - \frac{(d - \delta^*)}{\sigma_{treat}} - \Phi^{-1}(y)\right]\right), \quad 0 < y < 1.$$

Note that if n_0 and n_1 are the planned treatment arm sample sizes from a frequentist power calculation as described in Section 2.1.1 above, then, if $d = \delta_A$,

$$-z_{1-\alpha} - \frac{(d - \delta^*)}{\sigma_{treat}} = \Phi^{-1}(y) = \Phi^{-1}(1 - \beta) \quad \Rightarrow \quad P(RPR \leq y) = 0.5, \quad y = 1 - \beta.$$

Working example (continued)

With the above formula we calculate the probability $P(RPR > \gamma)$, $0 < \gamma < 1$, for the SAFE-SSPE study. We use an enthusiastic ($m = 6.6$), an informative ($m = 25$) and a noninformative prior ($m = 0.5$) prior, all centered on $\delta = 0$.

```
# gamma range
gamma <- seq(0.01, 0.99, 0.01)


# Centered on p1-p0
prior_mean <- 0
m_range <- c(0.5, 6.6, 25)
n_0_range <- n_0
data_rpr <- expand.grid(gamma, m_range, n_0_range)
names(data_rpr) <- c("gamma", "m_range", "n_0_range")
```

```r
data_rpr$n_1_range <- a * data_rpr$n_0_range
data_rpr$sigma_treat <- sqrt(sd_0^2/data_rpr$n_0_range + sd_1^2/data_rpr$n_1_range)
data_rpr$sigma_prior <- sqrt(sd_0^2/data_rpr$m_range + sd_1^2/data_rpr$m_range)

data_rpr$p_rpr <- pnorm(-qnorm(1 - alpha) * data_rpr$sigma_treat/data_rpr$sigma_prior -
    (1/data_rpr$sigma_prior) * (prior_mean - delta_star) -
      (data_rpr$sigma_treat/data_rpr$sigma_prior) *
    qnorm(data_rpr$gamma))

data_rpr$type <- NA
data_rpr$type[data_rpr$m_range == 0.5] <- "Noninformative"
data_rpr$type[data_rpr$m_range == 6.6] <- "Enthusiastic"
data_rpr$type[data_rpr$m_range == 25] <- "Informative"

# Centered on noninferiority margin
prior_mean <- delta_star
m_range <- c(6.6)
n_0_range <- n_0
data_rpr_skep <- expand.grid(gamma, m_range, n_0_range)
names(data_rpr_skep) <- c("gamma", "m_range", "n_0_range")
data_rpr_skep$n_1_range <- a * data_rpr_skep$n_0_range
data_rpr_skep$sigma_treat <- sqrt(sd_0^2/data_rpr_skep$n_0_range +
    sd_1^2/data_rpr_skep$n_1_range)
data_rpr_skep$sigma_prior <- sqrt(sd_0^2/data_rpr_skep$m_range +
    sd_1^2/data_rpr_skep$m_range)

data_rpr_skep$p_rpr <- pnorm(-qnorm(1 - alpha) *
                               data_rpr_skep$sigma_treat/data_rpr_skep$sigma_prior -
    (1/data_rpr_skep$sigma_prior) * (prior_mean - delta_star) -
    (data_rpr_skep$sigma_treat/data_rpr_skep$sigma_prior) * qnorm(data_rpr_skep$gamma))
```

```
data_rpr_skep$type <- "Skeptical"


data_rpr <- rbind(data_rpr, data_rpr_skep)


data_rpr$type <- factor(data_rpr$type, levels = c("Enthusiastic",
    "Skeptical", "Informative", "Noninformative"))


ggplot(data_rpr, aes(x = gamma, y = p_rpr, colour = type)) +
    geom_line(linewidth = 1) + theme_bw() + theme(panel.grid.minor = element_blank()) +
    scale_colour_manual("Prior type", values = c("purple", "orange",
        "blue", "darkred")) + scale_y_continuous(breaks = seq(0,
    1, 0.1)) + scale_x_continuous(breaks = seq(0, 1, 0.2)) +
    labs(caption = str_glue("Calculated based on a planned total sample size of ",
        round(n_0_range + a * n_0_range, 0), ".")) + xlab("Threshold gamma") +
    ylab("Probability that RPR is greater than threshold gamma")
```


Calculated based on a planned total sample size of 200.
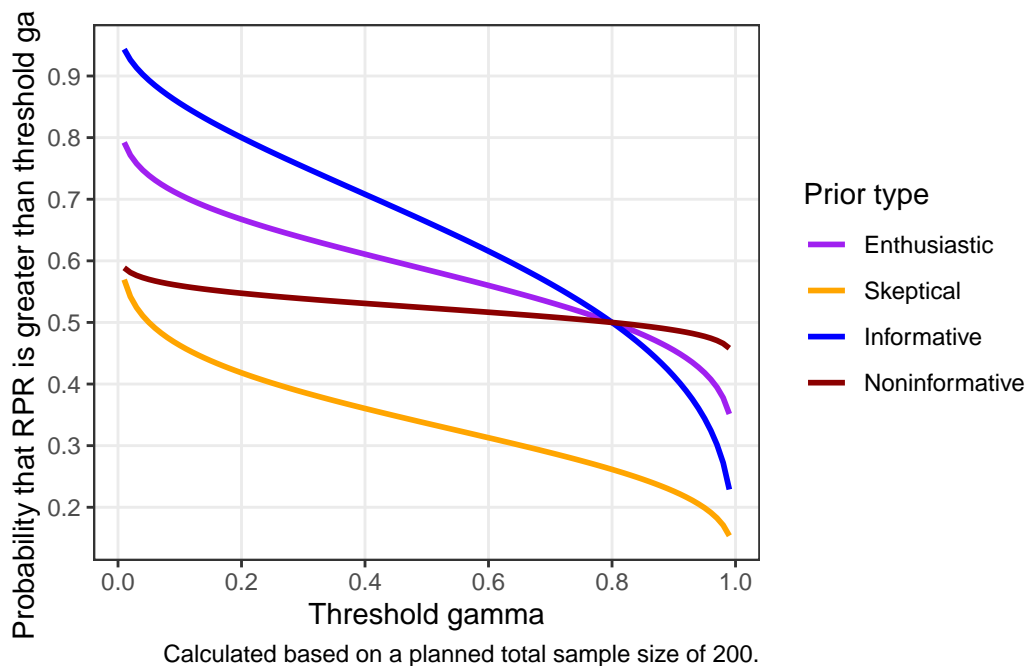
For a specific threshold, say $\gamma = 0.6$, and varying 'prior sample sizes' m we obtain

```
gamma <- 0.6


# Centered on p1-p0
prior_mean <- 0


m_range <- c(0.5, 6.6, 25)
n_0_range <- seq(0.01, 300, by = 1)


data_rpr <- expand.grid(m_range, n_0_range)
names(data_rpr) <- c("m_range", "n_0_range")
data_rpr$n_1_range <- a * data_rpr$n_0_range
data_rpr$sigma_treat <- sqrt(sd_0^2/data_rpr$n_0_range + sd_1^2/data_rpr$n_1_range)
data_rpr$sigma_prior <- sqrt(sd_0^2/data_rpr$m_range + sd_1^2/data_rpr$m_range)


data_rpr$p_rpr <- pnorm(data_rpr$sigma_treat/data_rpr$sigma_prior *
    (-qnorm(1 - alpha) - (1/data_rpr$sigma_treat) * (prior_mean -
        delta_star) - qnorm(gamma)))


data_rpr$type <- NA
data_rpr$type[data_rpr$m_range == 0.5] <- "Noninformative"
data_rpr$type[data_rpr$m_range == 6.6] <- "Enthusiastic"
data_rpr$type[data_rpr$m_range == 25] <- "Informative"



# Centered on noninferiority margin
prior_mean <- delta_star
m_range <- c(6.6)
n_0_range <- seq(0.01, 300, by = 1)
```

```r
data_rpr_skep <- expand.grid(m_range, n_0_range)
names(data_rpr_skep) <- c("m_range", "n_0_range")
data_rpr_skep$n_1_range <- a * data_rpr_skep$n_0_range
data_rpr_skep$sigma_treat <- sqrt(sd_0^2/data_rpr_skep$n_0_range +
    sd_1^2/data_rpr_skep$n_1_range)
data_rpr_skep$sigma_prior <- sqrt(sd_0^2/data_rpr_skep$m_range +
    sd_1^2/data_rpr_skep$m_range)

data_rpr_skep$p_rpr <- pnorm(data_rpr_skep$sigma_treat/data_rpr_skep$sigma_prior *
    (-qnorm(1 - alpha) - (1/data_rpr_skep$sigma_treat) * (prior_mean -
        delta_star) - qnorm(gamma)))

data_rpr_skep$type <- "Skeptical"

data_rpr <- rbind(data_rpr, data_rpr_skep)

data_rpr$type <- factor(data_rpr$type, levels = c("Enthusiastic",
    "Skeptical", "Informative", "Noninformative"))

ggplot(data_rpr, aes(x = n_1_range + n_0_range, y = p_rpr, colour = type)) +
    geom_line(linewidth = 1) + theme_bw() + theme(panel.grid.minor = element_blank()) +
    scale_colour_manual("Prior type", values = c("purple", "orange",
        "blue", "darkred")) + xlab("Planned total sample size") +
    ylab(str_glue("Probability that RPR is greater than ", gamma *
        100, "%")) + scale_x_continuous(breaks = c(0, 100, 200,
    300, 400), limits = c(0, 400)) + geom_vline(xintercept = 200,
    linetype = "dashed") + scale_y_continuous(breaks = seq(0,
    1, 0.1))
```
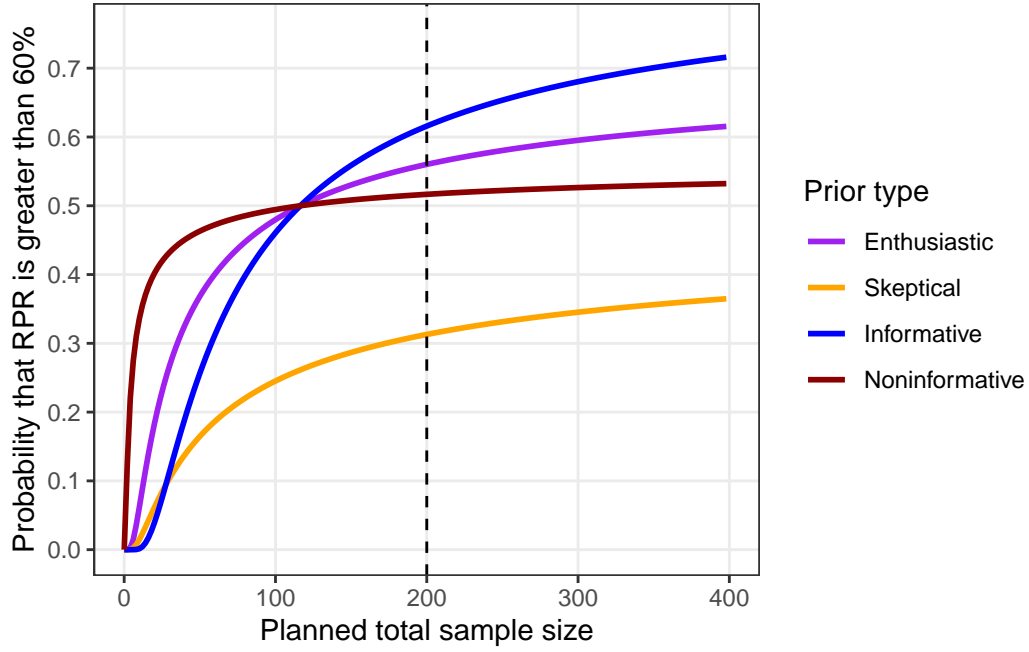
Note that the average power AP integrates over the whole Δ range. This might include also 'non-favorable' regions. To see that one can decompose AP as follows (see [1], [5]):

$$AP = \overbrace{P(D \le D_{suc}^{\delta^*}, \Delta > \delta^*)}^{(1)} + \overbrace{P(D \le D_{suc}^{\delta^*}, 0 < \Delta \le \delta^*)}^{(2)} + \overbrace{P(D \le D_{suc}^{\delta^*}, \Delta \le 0)}^{(3)}$$

where

- (1) Probability of Type-I error,
- (2) 'Non-inferior, but treatment effect not relevant',
- (3) 'Non-inferior, treatment effect relevant'.

Spiegelhalter et al. highlights that $AP \approx P(D \le D_{suc}^{\delta^*}, \Delta \le 0)$ because the type-I error is often small and one has strong believe for the alternative hypothesis [3]. [1] and [6] discuss the relevance of the AP decomposition. For example, pharmaceutical companies might (1)+(2)+(3) taking into account short-term risk, wheras regulators are interested in (1) or (1)+(2), that is non-inferior outcomes with relevant treatment effects.

For the non-inferiority setting we are interested in (2)+(3), that is $\Delta \leq \delta^*$:

$$P(D \leq D_{suc}^{\delta^*}, \Delta \leq \delta^*) = P(D \leq D_{suc}^{\delta^*}|\Delta \leq \delta^*)P(\Delta \leq \delta^*) = \underbrace{E\left[P_{\Delta \leq \delta^*}(D \leq D_{suc}^{\delta^*})\right]}_{EP} P(\Delta \leq \delta^*),$$

Kunzmann et al. denote EP the **'expected power'** [1]. Note that

$$\underbrace{P(D \leq D_{suc}^{\delta^*}, \Delta \leq \delta^*)}_{PAP} = \underbrace{E\left[P_{\Delta \leq \delta^*}(D \leq D_{suc}^{\delta^*})\right]}_{EP} \underbrace{P(\Delta \leq \delta^*)}_{constant}.$$

Spiegelhalter calls $P(D \leq D_{suc}^{\delta^*}, \Delta \leq \delta^*)$ the **'prior adjusted power'** (PAP).

The AP decomposition can be visualised using the posterior predictive distribution. Let $p(\tilde{\delta})$ be the pdf of the posterior predictive distribution then

$$p(\tilde{\delta}, \delta) = N_2\left(\begin{pmatrix} d \\ d \end{pmatrix}, \begin{pmatrix} \sigma_{treat}^2 + \sigma_{prior}^2 & \sigma_{prior}^2 \\ \sigma_{prior}^2 & \sigma_{prior}^2 \end{pmatrix}\right),$$

see formula (2.11) in [5].

Working example (continued)

For the SAFE-SSPE study the bivariate scatterplot of $p(\tilde{\delta}, \delta)$ under an enthusiastic prior can be visualised as:

```r
library(mvtnorm)
library(tidyverse)
library(ggplot2)


delta_star <- 0.035
prior_mean <- 0
m <- 6.6
```

```r
sigma_sim <- matrix(c((sd_0^2/n_0 + sd_1^2/n_1 + (sd_1^2 + sd_0^2)/m),
    (sd_1^2 + sd_0^2)/m, (sd_1^2 + sd_0^2)/m, (sd_1^2 + sd_0^2)/m),
    nrow = 2, ncol = 2, byrow = T)


set.seed(1)
data_sim <- data.frame(rmvnorm(n = 10000, mean = c(prior_mean,
    prior_mean), sigma_sim))
names(data_sim) <- c("delta_pred", "delta")


data_sim$region <- ifelse(data_sim$delta <= 0 & data_sim$delta_pred <=
    -qnorm(1 - alpha) * sqrt(sd_1^2/n_1+sd_0^2/n_0) - (prior_mean - delta_star),
    1, 0)
data_sim$region <- ifelse(data_sim$delta > 0 & data_sim$delta <=
    delta_star & data_sim$delta_pred <= -qnorm(1 - alpha) * sqrt(sd_1^2/n_1+sd_0^2/n_0) -
    (prior_mean - delta_star), 2, data_sim$region)
data_sim$region <- ifelse(data_sim$delta > delta_star & data_sim$delta_pred <=
    -qnorm(1 - alpha) * sqrt(sd_1^2/n_1+sd_0^2/n_0) - (prior_mean - delta_star),
    3, data_sim$region)


data_sim$region <- factor(data_sim$region, levels = 0:3, labels = c("'Not significant'",
    "(3)", "(2)", "(1)"))


ggplot(data_sim, aes(x = delta, y = delta_pred, colour = factor(region))) +
    geom_point(size = 0.3) + theme_bw() + theme(panel.grid.minor = element_blank()) +
    geom_vline(xintercept = 0.035, linetype = "dashed") + geom_hline(yintercept = -qnorm(1 -
    alpha) * sqrt(sd_1^2/n_1+sd_0^2/n_0) - (prior_mean - delta_star), linetype = "dotted") +
    ylab("Predictive distribution of Delta") + xlab("Delta") +
    scale_color_brewer("Region", palette = "Reds") + scale_x_continuous(breaks = c(-0.2,
    -0.1, 0, 0.035, 0.2), labels = c(-0.2, -0.1, 0, 0.035, 0.2)) +
    labs(caption = "Dashed line: Noninferiority margin.\nDotted line: Upper CI from predicted
```
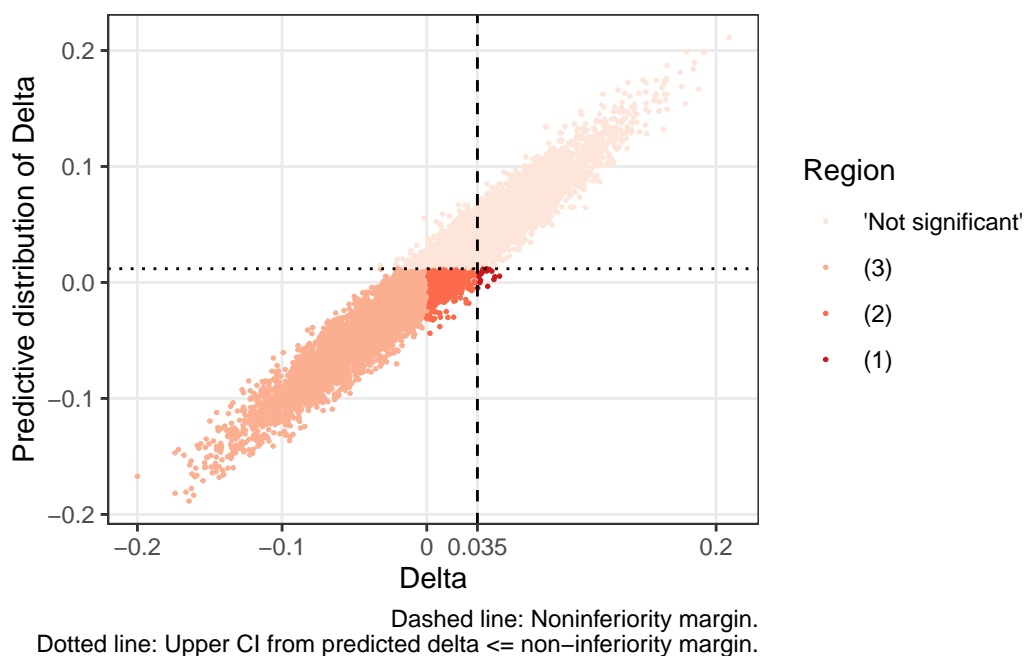
Dashed line: Noninferiority margin.
Dotted line: Upper CI from predicted delta <= non−inferiority margin.

```
data_output <- data.frame(data_sim %>%

    group_by(region) %>%

    summarise(prop = n()/nrow(data_sim)))


data_output
```

	region	prop
1	'Not significant'	0.4148
2	(3)	0.4909
3	(2)	0.0920
4	(1)	0.0023

From the above values the average power can be calculated as (1) 0.0023 + (2) 0.092 + (3) 0.4909, which is equal to 0.5852. This is the value we reported above (59%).

The results of EP, PAP and AP are shown in the table below:

```r
delta_star <- 0.035
prior_mean <- 0
m <- 6.6


set.seed(1)


sd_prior <- sqrt((sd_1^2 + sd_0^2))/sqrt(m)
draws <- rnorm(10000, mean = prior_mean, sd = sd_prior)


power_classic <- pnorm(-qnorm(1 - alpha) - sqrt(n_0 * n_1)/sqrt((n_0 *
    sd_1^2 + n_1 * sd_0^2)) * (draws - delta_star))


data_ep <- data.frame(ep = mean(power_classic[draws <= delta_star]),
    pap = mean(power_classic[draws <= delta_star]) * pnorm(delta_star,
        mean = prior_mean, sd = sd_prior), ap = mean(power_classic),
    const = pnorm(delta_star, mean = prior_mean, sd = sd_prior),
    type = "Skeptical")


set.seed(1)
prior_mean <- delta_star
m <- 6.6
draws <- rnorm(10000, mean = prior_mean, sd = sd_prior)


power_classic <- pnorm(-qnorm(1 - alpha) - sqrt(n_0 * n_1)/sqrt((n_0 *
    sd_1^2 + n_1 * sd_0^2)) * (draws - delta_star))


data_ep <- rbind(data_ep, data.frame(ep = mean(power_classic[draws <=
    delta_star]), pap = mean(power_classic[draws <= delta_star]) *
    pnorm(delta_star, mean = prior_mean, sd = sd_prior), ap = mean(power_classic),
    const = pnorm(delta_star, mean = prior_mean, sd = sd_prior),
```

```r
    type = "Enthusiastic"))


prior_mean <- 0
m <- 25
set.seed(1)
draws <- rnorm(10000, mean = prior_mean, sd = sd_prior)


power_classic <- pnorm(-qnorm(1 - alpha) - sqrt(n_0 * n_1)/sqrt((n_0 *
    sd_1^2 + n_1 * sd_0^2)) * (draws - delta_star))


data_ep <- rbind(data_ep, data.frame(ep = mean(power_classic[draws <=
    delta_star]), pap = mean(power_classic[draws <= delta_star]) *
    pnorm(delta_star, mean = prior_mean, sd = sd_prior), ap = mean(power_classic),
    const = pnorm(delta_star, mean = prior_mean, sd = sd_prior),
    type = "Informative"))


prior_mean <- 0
m <- 0.5
set.seed(1)
draws <- rnorm(1e+05, mean = prior_mean, sd = sd_tilde/sqrt(0.5))


power_classic <- pnorm(-qnorm(1 - alpha) - sqrt(n_0 * n_1)/sqrt((n_0 *
    sd_1^2 + n_1 * sd_0^2)) * (draws - delta_star))


data_ep <- rbind(data_ep, data.frame(ep = mean(power_classic[draws <=
    delta_star]), pap = mean(power_classic[draws <= delta_star]) *
    pnorm(delta_star, mean = prior_mean, sd = sd_prior), ap = mean(power_classic),
    const = pnorm(delta_star, mean = prior_mean, sd = sd_prior),
    type = "Noninformative"))
```

```
data_ep$ep <- round(data_ep$ep, 4)

data_ep$ap <- round(data_ep$ap, 4)

data_ep$pap <- round(data_ep$pap, 4)

data_ep$const <- round(data_ep$const, 4)


data_ep
```

```
      ep    pap     ap  const              type
1 0.7930 0.5857 0.5872 0.7386          Skeptical
2 0.6740 0.3370 0.3437 0.5000       Enthusiastic
3 0.7930 0.5857 0.5872 0.7386        Informative
4 0.9186 0.6785 0.5233 0.7386     Noninformative
```

2.2.1.3 Proper Bayesian approach: Prior on the treatment effect

A proper Bayesian approach uses the posterior distribution to define 'a successful trial result'. Remember that $D = \bar{p}_1 - \bar{p}_0$ with $D \sim N(\delta, \sigma_{treat}^2)$. Suppose that $\Delta \sim N(d, \sigma_{prior}^2)$ is an analysis prior, then the posterior distribution is given as

$$\Delta | D \sim N\left(\frac{\frac{d}{\sigma_{prior}^2} + \frac{D}{\sigma_{treat}^2}}{\frac{1}{\sigma_{prior}^2} + \frac{1}{\sigma_{treat}^2}}, \frac{1}{\frac{1}{\sigma_{prior}^2} + \frac{1}{\sigma_{treat}^2}} \right) = N\left(\frac{\sigma_{treat}^2 d + \sigma_{prior}^2 D}{\sigma_{treat}^2 + \sigma_{prior}^2}, \frac{\sigma_{treat}^2 \sigma_{prior}^2}{\sigma_{treat}^2 + \sigma_{prior}^2} \right),$$

see for example [8].

Special case

If $n_0 = n_1 = n$ and $\sigma_1^2 = \sigma_0^2 = \sigma^2$, then $\sigma_{treat}^2 = \frac{2\sigma^2}{n}$ and $\sigma_{prior}^2 = \frac{2\sigma^2}{m}$, and the formula above reduces to

$$\Delta|D \sim N\left(\frac{m\delta + nD}{n+m}, \frac{2\sigma^2}{n+m}\right).$$

A trial success can then be defined as

$$P(\Delta \leq \delta^*|D) = 1 - \epsilon,$$

where ϵ is small, say $\epsilon = 0.05$.

Similar to the frequentist approach, one is interested whether the upper $(1-\epsilon)$ credible interval is smaller than the non-inferiority margin, that is

$$\frac{\sigma_{treat}^2 d + \sigma_{prior}^2 D}{\sigma_{treat}^2 + \sigma_{prior}^2} + z_{1-\epsilon}\frac{\sigma_{treat}\sigma_{prior}}{\sqrt{\sigma_{treat}^2 + \sigma_{prior}^2}} \leq \delta^*.$$

A simple algebraic step gives

$$D \leq -z_{1-\epsilon}\frac{\sigma_{treat}}{\sigma_{prior}}\sqrt{\sigma_{treat}^2 + \sigma_{prior}^2} + \delta^*\left(1 + \frac{\sigma_{treat}^2}{\sigma_{prior}^2}\right) - \frac{\sigma_{treat}^2}{\sigma_{prior}^2}d.$$

Similar to the frequentist approach we can denote $D_{suc}^{d,\delta^*} = -z_{1-\epsilon}\frac{\sigma_{treat}}{\sigma_{prior}}\sqrt{\sigma_{treat}^2 + \sigma_{prior}^2} + \delta^*\left(1 + \frac{\sigma_{treat}^2}{\sigma_{prior}^2}\right) - \frac{\sigma_{treat}^2}{\sigma_{prior}^2}d$ as the required risk difference for a successful rejection of the null hypothesis in the Bayesian setting.

Thus, since $D \sim N(\delta, \sigma_{treat}^2)$,

$$P(D \leq D_{suc}^{d,\delta^*}|\delta) = \Phi\left(-z_{1-\epsilon}\sqrt{1 + \frac{\sigma_{treat}^2}{\sigma_{prior}^2}} - \frac{1}{\sigma_{treat}}\left[\delta - \delta^*\left\{1 + \frac{\sigma_{treat}^2}{\sigma_{prior}^2}\right\}\right] - \frac{\sigma_{treat}}{\sigma_{prior}^2}d\right).$$

This is the **Bayesian probability to reject** (or Bayesian power) under an (assumed) known true treatment effect δ. Note that this is a conditional probability on δ.

Special case

If $n_0 = n_1 = n$ and $\sigma_1^2 = \sigma_0^2 = \sigma^2$, then $\sigma_{treat}^2 = \frac{2\sigma^2}{n}$ and $\sigma_{prior}^2 = \frac{2\sigma^2}{m}$, and the formula above reduces to

$$P(D \le D_{suc}^{d,\delta^*}|\delta) = \Phi\left(-z_{1-\epsilon}\sqrt{\frac{n+m}{n}} - \frac{m}{\sqrt{2n\sigma^2}}d - \sqrt{\frac{n}{2n\sigma^2}}\left\{\delta - \delta^*\left(\frac{n+m}{n}\right)\right\}\right).$$

Working example (continued)

We derive the Bayesian probability to reject for the SAFE-SSPE study for different δ values and analysis priors.

```
# Delta range
delta <- seq(-0.025, 0.05, 0.001)


# Epsilon
epsilon <- 0.05


# Enthusiastic prior
prior_mean <- 0
m <- 6.6


ap_bayes <- pnorm(-qnorm(1 - epsilon) * (sqrt(1 + m * (n_0 *
    sd_1^2 + n_1 * sd_0^2)/(n_1 * n_0 * (sd_1^2 + sd_0^2)))) -
    (m * sqrt(n_0 * sd_1^2 + n_1 * sd_0^2))/(sqrt(n_1 * n_0) *
        (sd_1^2 + sd_0^2)) * prior_mean - sqrt((n_1 * n_0)/((n_0 *
    sd_1^2 + n_1 * sd_0^2))) * (delta - delta_star * (1 + (m *
    (n_0 * sd_1^2 + n_1 * sd_0^2))/(n_1 * n_0 * (sd_1^2 + sd_0^2)))))
```

```r
data_power <- data.frame(delta, y = ap_bayes, type = "Bayes: Enthusiastic")


# Skeptical prior
prior_mean <- 0.035
m <- 6.6


ap_bayes <- pnorm(-qnorm(1 - epsilon) * (sqrt(1 + m * (n_0 *
    sd_1^2 + n_1 * sd_0^2)/(n_1 * n_0 * (sd_1^2 + sd_0^2))))) -
    (m * sqrt(n_0 * sd_1^2 + n_1 * sd_0^2))/(sqrt(n_1 * n_0) *
        (sd_1^2 + sd_0^2)) * prior_mean - sqrt((n_1 * n_0)/((n_0 *
    sd_1^2 + n_1 * sd_0^2))) * (delta - delta_star * (1 + (m *
    (n_0 * sd_1^2 + n_1 * sd_0^2))/(n_1 * n_0 * (sd_1^2 + sd_0^2)))))


data_power <- rbind(data_power, data.frame(delta, y = ap_bayes,
    type = "Bayes: Skeptical"))


# Informative prior
prior_mean <- 0
m <- 25


ap_bayes <- pnorm(-qnorm(1 - epsilon) * (sqrt(1 + m * (n_0 *
    sd_1^2 + n_1 * sd_0^2)/(n_1 * n_0 * (sd_1^2 + sd_0^2))))) -
    (m * sqrt(n_0 * sd_1^2 + n_1 * sd_0^2))/(sqrt(n_1 * n_0) *
        (sd_1^2 + sd_0^2)) * prior_mean - sqrt((n_1 * n_0)/((n_0 *
    sd_1^2 + n_1 * sd_0^2))) * (delta - delta_star * (1 + (m *
    (n_0 * sd_1^2 + n_1 * sd_0^2))/(n_1 * n_0 * (sd_1^2 + sd_0^2)))))


data_power <- rbind(data_power, data.frame(delta, y = ap_bayes,
    type = "Bayes: Informative"))
```

```r
# Noninformative prior
prior_mean <- 0
m <- 0.5

ap_bayes <- pnorm(-qnorm(1 - epsilon) * (sqrt(1 + m * (n_0 *
    sd_1^2 + n_1 * sd_0^2)/(n_1 * n_0 * (sd_1^2 + sd_0^2)))) -
    (m * sqrt(n_0 * sd_1^2 + n_1 * sd_0^2))/(sqrt(n_1 * n_0) *
        (sd_1^2 + sd_0^2)) * prior_mean - sqrt((n_1 * n_0)/((n_0 *
    sd_1^2 + n_1 * sd_0^2))) * (delta - delta_star * (1 + (m *
    (n_0 * sd_1^2 + n_1 * sd_0^2))/(n_1 * n_0 * (sd_1^2 + sd_0^2)))))

data_power <- rbind(data_power, data.frame(delta, y = ap_bayes,
    type = "Bayes: Noninformative"))


# Frequentist
y_freq <- pnorm(-(delta - delta_star) * sqrt(n_1 * n_0)/sqrt(n_0 *
    sd_1^2 + n_1 * sd_0^2) - qnorm(1 - alpha))
data_power <- rbind(data_power, data.frame(delta, y = y_freq,
    type = "Frequentist"))

data_power$type <- factor(data_power$type, levels = c("Bayes: Enthusiastic",
    "Bayes: Skeptical", "Bayes: Informative", "Bayes: Noninformative",
    "Frequentist"))


ggplot(data_power, aes(x = delta, y = y, colour = type)) + geom_line() +
    theme_bw() + theme(panel.grid.minor = element_blank()) +
    scale_colour_manual("Type", values = c("purple", "orange",
        "blue", "darkred", "green")) + ylab("Probability to reject") +
```
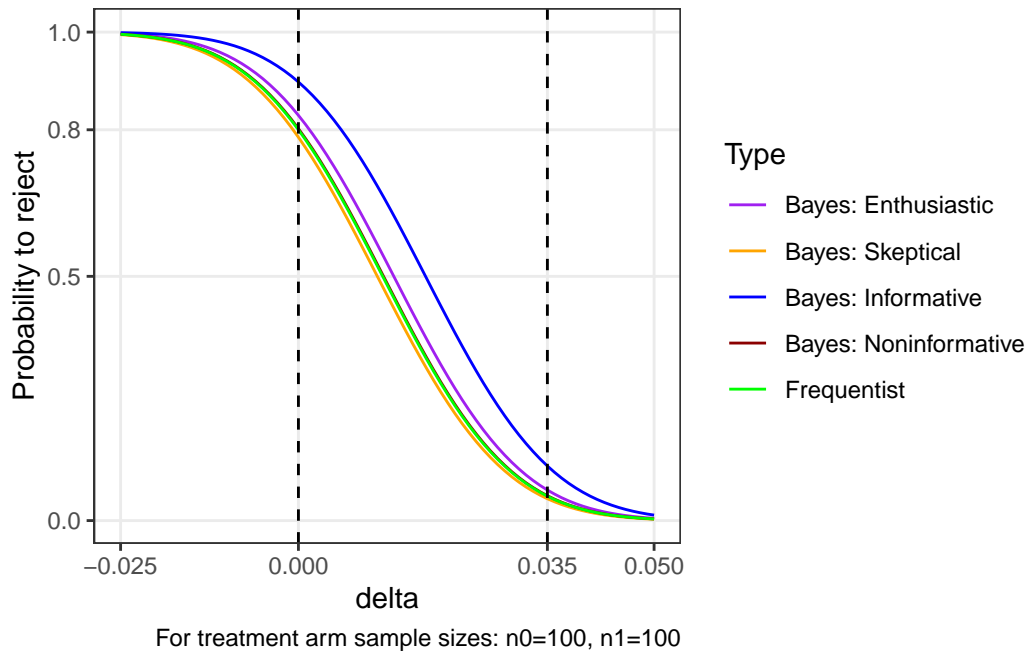
```
ylab("Probability to reject") + scale_x_continuous(breaks = c(-0.025,
0, 0.035, 0.05)) + scale_y_continuous(breaks = c(0, 0.5,
0.8, 1)) + geom_vline(xintercept = 0, linetype = "dashed") +
geom_vline(xintercept = 0.035, linetype = "dashed") +
labs(caption=str_glue("For treatment arm sample sizes: n0=",
round(n_0, 0), ", n1=", round(n_1, 0)))
```


For treatment arm sample sizes: n0=100, n1=100

```
data_power$y <- round(data_power$y, 2)
data_power %>%
    filter(delta %in% c("0", "0.035"))
```

```
  delta    y                   type
1 0.000 0.83    Bayes: Enthusiastic
2 0.035 0.06    Bayes: Enthusiastic
3 0.000 0.78       Bayes: Skeptical
4 0.035 0.04       Bayes: Skeptical
5 0.000 0.90      Bayes: Informative
```

```
6  0.035 0.11     Bayes: Informative
7  0.000 0.80 Bayes: Noninformative
8  0.035 0.05 Bayes: Noninformative
9  0.000 0.80          Frequentist
10 0.035 0.05          Frequentist
```

The Bayesian probability to reject $H_0 : \delta > \delta^*$ given $\delta = p_1 - p_0 = 0$ and an informative prior is 90%. This is higher than the frequentist probability to reject of 80% given $\delta = p_1 - p_0 = 0$. In contrast, the probability to reject $H_0 : \delta > \delta^*$ for $\delta = 0.035$ under an informative prior is 11%. This is higher than the frequentist 'type-I error' of 5%. The probability to reject under the null hypothesis is higher for the Bayesian approach under an informative prior because the prior has substantial believe in non-inferiority.

The average (marginal) Bayesian probability to reject (BAP) can be calculated as

$$
BAP = \int_{-\infty}^{-z_{1-\epsilon}\frac{\sigma_{treat}}{\sigma_{prior}}\sqrt{\sigma_{treat}^2+\sigma_{prior}^2}+\delta^*\left(1+\frac{\sigma_{treat}^2}{\sigma_{prior}^2}\right)-\frac{\sigma_{treat}^2}{\sigma_{prior}^2}d} f(\tilde{\delta})d\tilde{\delta}
$$

$$
= \Phi\left(-z_{1-\epsilon}\frac{\sigma_{treat}}{\sigma_{prior}}\frac{\sqrt{\sigma_{treat}^2+\sigma_{prior}^2}}{\sqrt{\sigma_{treat}^2+\sigma_{prior}^2}} + \frac{\delta^*}{\sqrt{\sigma_{treat}^2+\sigma_{prior}^2}}\left\{1+\frac{\sigma_{treat}^2}{\sigma_{prior}^2}\right\}\right.
$$

$$
\left. -\frac{d}{\sqrt{\sigma_{treat}^2+\sigma_{prior}^2}}\left\{1+\frac{\sigma_{treat}^2}{\sigma_{prior}^2}\right\}\right)
$$

$$
= \Phi\left(-z_{1-\epsilon}\frac{\sigma_{treat}}{\sigma_{prior}} - \frac{\sqrt{\sigma_{treat}^2+\sigma_{prior}^2}}{\sigma_{prior}^2}(d-\delta^*)\right),
$$

since the posterior predictive distribution $\tilde{D} \sim N(d, \sigma_{treat}^2 + \sigma_{prior}^2)$.

Special case

36

If $n_0 = n_1 = n$ and $\sigma_1^2 = \sigma_0^2 = \sigma^2$, then $\sigma_{treat}^2 = \frac{2\sigma^2}{n}$ and $\sigma_{prior}^2 = \frac{2\sigma^2}{m}$, and the formula above reduces to

$$BAP = -z_{1-\epsilon}\sqrt{\frac{m}{n}} - \sqrt{\frac{(m+n)m}{2n\sigma^2}}(d - \delta^*)$$

Working example (continued)

We derive the average Bayesian probability to reject for the SAFE-SSPE study.

```
### Hybrid AP


sigma_treat <- sqrt((sd_0^2/n_0 + sd_1^2/n_1))

digit_round <- 4


# Enthusiastic prior

m <- 6.6

prior_mean <- 0

sigma_prior <- sqrt((sd_0^2 + sd_1^2))/sqrt(m)


AP <- pnorm(1/sigma_prior * (-qnorm(1 - alpha) * sigma_treat -

    (prior_mean - delta_star)))


data_output <- data.frame(type = "Enthusiastic", n_0, n_1, AP = round(AP,

    digit_round))


# Skeptical prior

m <- 6.6

prior_mean <- delta_star

sigma_prior <- sqrt((sd_0^2 + sd_1^2))/sqrt(m)
```

```r
AP <- pnorm(1/sigma_prior * (-qnorm(1 - alpha) * sigma_treat -
    (prior_mean - delta_star)))


data_output <- rbind(data_output, data.frame(type = "Skeptical",
    n_0, n_1, AP = round(AP, digit_round)))


# Informative prior
m <- 25
prior_mean <- 0
sigma_prior <- sqrt((sd_0^2 + sd_1^2))/sqrt(m)


AP <- pnorm(1/sigma_prior * (-qnorm(1 - alpha) * sigma_treat -
    (prior_mean - delta_star)))


data_output <- rbind(data_output, data.frame(type = "Informative",
    n_0, n_1, AP = round(AP, digit_round)))


# Noninformative prior
m <- 0.5
prior_mean <- 0
sigma_prior <- sqrt((sd_0^2 + sd_1^2))/sqrt(m)


AP <- pnorm(1/sigma_prior * (-qnorm(1 - alpha) * sigma_treat -
    (prior_mean - delta_star)))


data_output <- rbind(data_output, data.frame(type = "Noninformative",
    n_0, n_1, AP = round(AP, digit_round)))


data_output <- data_output %>%
```

```
    select(type, n_0, n_1, AP)


### Bayesian AP

sigma_treat <- sqrt((sd_0^2/n_0 + sd_1^2/n_1))


# Enthusiastic prior
prior_mean <- 0
m <- 6.6
sigma_prior <- sqrt((sd_0^2 + sd_1^2))/sqrt(m)


ap_bayes <- pnorm(-qnorm(1 - alpha) * sigma_treat/sigma_prior -
    sqrt(sigma_treat^2 + sigma_prior^2)/sigma_prior^2 * (prior_mean -
        delta_star))


data_output2 <- data.frame(type = "Enthusiastic", n_0, n_1, AP_bayes = round(ap_bayes,
    digit_round))


# Skeptical prior
prior_mean <- delta_star
m <- 6.6
sigma_prior <- sqrt((sd_0^2 + sd_1^2))/sqrt(m)


ap_bayes <- pnorm(-qnorm(1 - alpha) * sigma_treat/sigma_prior -
    sqrt(sigma_treat^2 + sigma_prior^2)/sigma_prior^2 * (prior_mean -
        delta_star))


data_output2 <- rbind(data_output2, data.frame(type = "Skeptical",
    n_0, n_1, AP_bayes = round(ap_bayes, digit_round)))
```

```r
# Informative prior
prior_mean <- 0
m <- 25
sigma_prior <- sqrt((sd_0^2 + sd_1^2))/sqrt(m)

ap_bayes <- pnorm(-qnorm(1 - alpha) * sigma_treat/sigma_prior -
    sqrt(sigma_treat^2 + sigma_prior^2)/sigma_prior^2 * (prior_mean -
        delta_star))

data_output2 <- rbind(data_output2, data.frame(type = "Informative",
    n_0, n_1, AP_bayes = round(ap_bayes, digit_round)))

# Noninformative prior
prior_mean <- 0
m <- 0.5
sigma_prior <- sqrt((sd_0^2 + sd_1^2))/sqrt(m)

ap_bayes <- pnorm(-qnorm(1 - alpha) * sigma_treat/sigma_prior -
    sqrt(sigma_treat^2 + sigma_prior^2)/sigma_prior^2 * (prior_mean -
        delta_star))

data_output2 <- rbind(data_output2, data.frame(type = "Noninformative",
    n_0, n_1, AP_bayes = round(ap_bayes, digit_round)))

data_output <- left_join(data_output, data_output2 %>%
    select(type, AP_bayes), by = "type")

data_output %>%
    select(type, n_0, n_1, AP_hybrid = AP, AP_bayes)
```

```
            type      n_0      n_1 AP_hybrid AP_bayes
1   Enthusiastic 99.93031 99.93031   0.5856   0.5937
2      Skeptical 99.93031 99.93031   0.3363   0.3363
3    Informative 99.93031 99.93031   0.6631   0.7149
4 Noninformative 99.93031 99.93031   0.5237   0.5239
```

The average Bayesian power under an informative prior is 72% compared to 66% from a hybrid approach.

2.2.1.4 Hybrid approach: Prior on event probabilities

In the former subsections we assumed that the prior was directly specified on the treatment effect. In this subsection we assume that that design prior is specified on the event probabilities p_i, $i = \{0, 1\}$. Suppose that the design priors on the event probabilities are beta distributed $\pi_i \sim Beta(a_i, b_i)$, $i = \{0, 1\}$. It is well known (see for example [3] or [5]) that the prior predictive distribution of the number of events R_i, $i = \{0, 1\}$, from n_i Bernoulli observations is beta-binomial distributed with $R_i \sim betabinom(r_i|n_i, a_i, b_i)$ and

$$E(R_i) = n_i \frac{a_i}{a_i + b_i}, \quad Var(R_i) = \frac{n_i a_i b_i (n_i + a_i + b_i)}{(a_i + b_i)^2 (a_i + b_i + 1)}.$$

Working example (continued)

For the SAFE-SSPE trial we specify the following design beta priors for the expected event probabilites $p_1 = p_0 = 0.01$.

Enthusiastic prior: The beta prior for the active treatment arm is centered at 0.01 (the expected event proportion) with $P(\pi_1 > 0.05) = 0.025$, that is, the probability that the prior is greater than the safety margin is 2.5%. The mean of the beta prior for the control arm is centered at 0.03 (the safety margin) with $P(\pi_0 > 0.05) = 0.05$.

- Parameters of beta prior for active treatment arm: $a_1 = 0.5$, $b_1 = 49.5$.

- Parameters of beta prior for control treatment arm: $a_0 = 7.2$, $b_0 = 232.8$.

```r
library(extraDistr)


p_1 <- 0.01
x <- seq(0.001, 0.999, 0.001)


## Enthusiastic prior
a_1 <- 0.5
b_1 <- (1 - p_1)/p_1 * a_1
a_0 <- 7.2
b_0 <- (1 - 0.03)/0.03 * a_0


prior_0 <- dbeta(x, a_0, b_0)
prior_1 <- dbeta(x, a_1, b_1)


prior_plot <- data.frame(x, prior_0, prior_1)
prior_plot_long <- pivot_longer(prior_plot, cols = c(prior_0, prior_1))
prior_plot_long$group <- ifelse(str_detect(prior_plot_long$name, "_0") ==
    T, "Treatment arm 0", "Treatment arm 1")


fig1 <- ggplot(prior_plot_long, aes(x = x, y = value, colour = group)) +
    geom_line(linewidth = 1.5) + theme_bw() + theme(panel.grid.minor = element_blank(),
    legend.position = "bottom", legend.direction = "horizontal") + scale_x_continuous(limits =
    0.1)) + ylab("Density") + labs(caption = str_glue("Assumed event probabilities: Arm 0 (p_0=
    p_0, "), ", "Arm 1 (p_1=", p_1, ")")) + scale_color_brewer("Treatment arm",
    palette = "Set2") + scale_linetype("Type") + ggtitle("Enthusiastic prior")


diff_prior <- data.frame(x = rbbinom(1e+06, size = ceiling(n_1), a_1,
    b_1)/ceiling(n_1) - rbbinom(1e+06, size = ceiling(n_0), a_0, b_0)/ceiling(n_0))
```
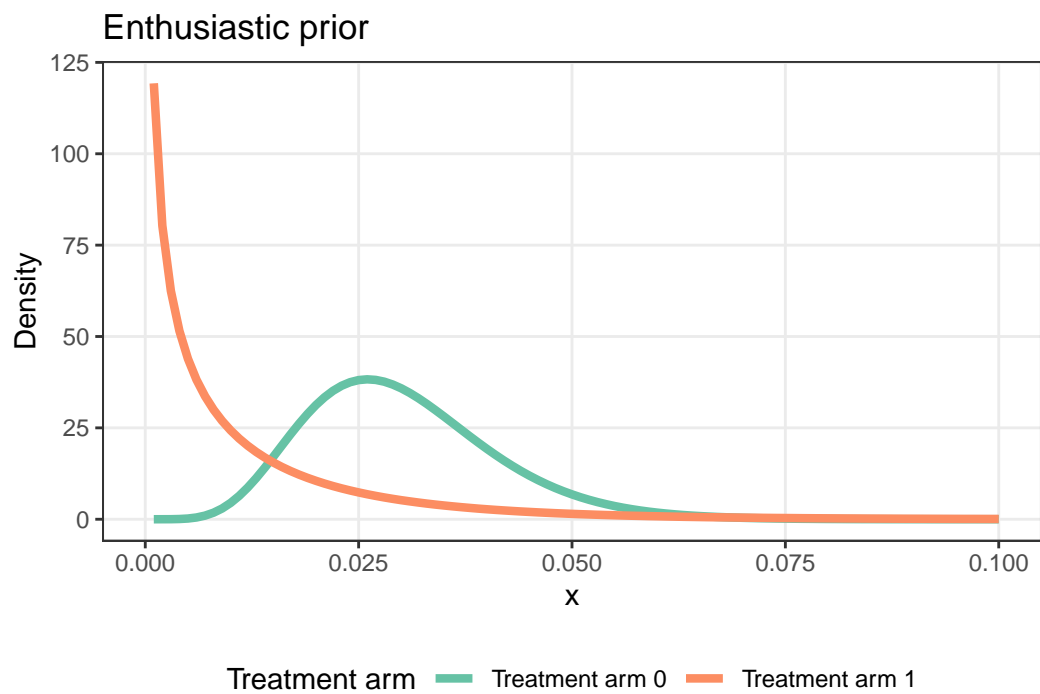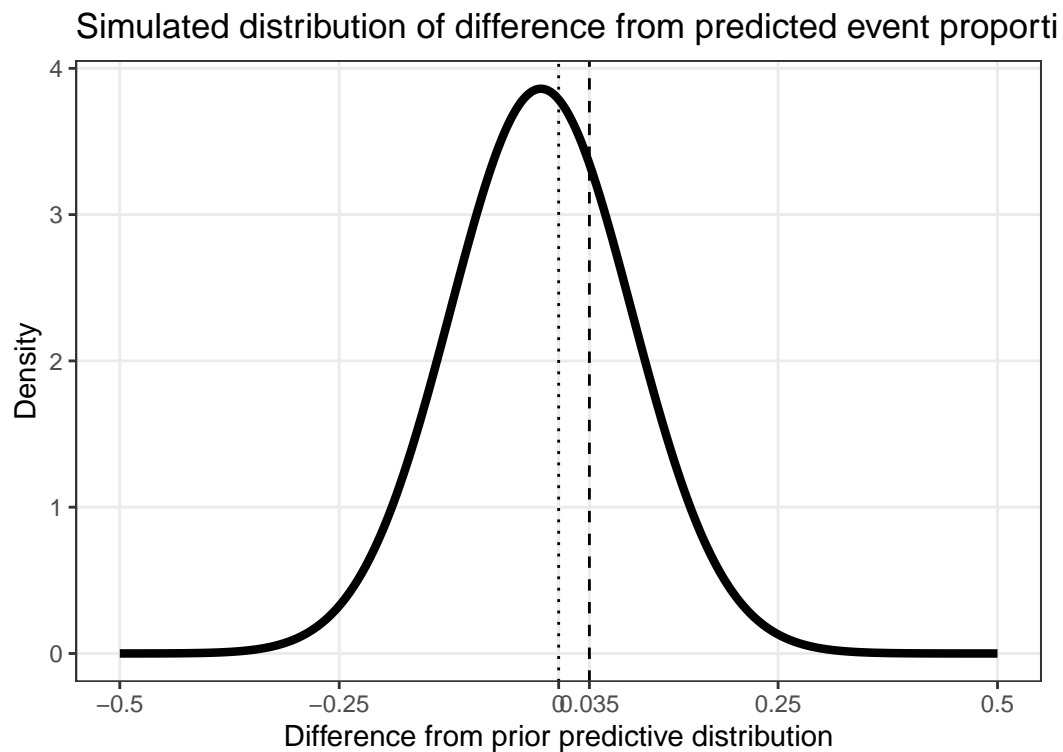
```r
fig2 <- ggplot(diff_prior, aes(x), group=x) + geom_density(linewidth = 1.5, bw=0.1) +
    theme_bw() + theme(panel.grid.minor = element_blank()) +
    xlab("Difference from prior predictive distribution") + ggtitle("Simulated distribution of
    ylab("Density") + geom_vline(xintercept=delta_star, linetype="dashed") +
    geom_vline(xintercept=0, linetype="dotted") +
    scale_x_continuous(breaks=c(-0.5, -0.25, 0, 0.035, 0.25, 0.5),
                       labels=c(-0.5, -0.25, 0, 0.035, 0.25, 0.5),
                       limits=c(-0.5, 0.5))


cowplot::plot_grid(fig1, fig2, align = "h", ncol = 1)
```

Enthusiastic prior

Treatment arm — Treatment arm 0 — Treatment arm 1

Assumed event probabilities: Arm 0 (p_0=0.01), Arm 1 (p_1=0.01)

Simulated distribution of difference from predicted event proporti

Skeptical prior: The beta prior for the active treatment arm is centered at 0.05 (the safety margin) with

$P(\pi_1 \leq 0.01) = 0.025$, that is the probability that the prior is smaller or equal than the expected event proportion is 2.5%. The mean of the beta prior for the control arm is is centered at 0.01 (the expected event proportion) with $P(\pi_0 > 0.05) = 0.025$.

- Parameters of beta prior for active treatment arm: $a_1 = 2.84$, $b_1 = 53.96$.
- Parameters of beta prior for control treatment arm: $a_i = 1.24$, $b_i = 122.76$.

```r
x <- seq(0.001, 0.999, 0.001)


# Skeptical
a_1 <- 2.84
b_1 <- (1 - 0.05)/0.05 * a_1
a_0 <- 1.24
b_0 <- (1 - 0.01)/0.01 * a_0


prior_0 <- dbeta(x, a_0, b_0)
prior_1 <- dbeta(x, a_1, b_1)


prior_plot <- data.frame(x, prior_0, prior_1)
prior_plot_long <- pivot_longer(prior_plot, cols = c(prior_0, prior_1))


prior_plot_long$group <- ifelse(str_detect(prior_plot_long$name, "_0") ==
    T, "Treatment arm 0", "Treatment arm 1")

fig1 <- ggplot(prior_plot_long, aes(x = x, y = value, colour = group)) +
    geom_line(linewidth = 1.5) + theme_bw() + theme(panel.grid.minor = element_blank(),
    legend.position = "bottom", legend.direction = "horizontal") + scale_x_continuous(limits =
    0.1)) + ylab("Density") + labs(caption = str_glue("Assumed event probabilities: Arm 0 (p_0=
    p_0, "), ", "Arm 1 (p_1=", p_1, ")")) + scale_color_brewer("Treatment arm",
    palette = "Set2") + scale_linetype("Type") + ggtitle("Skeptical prior")
```
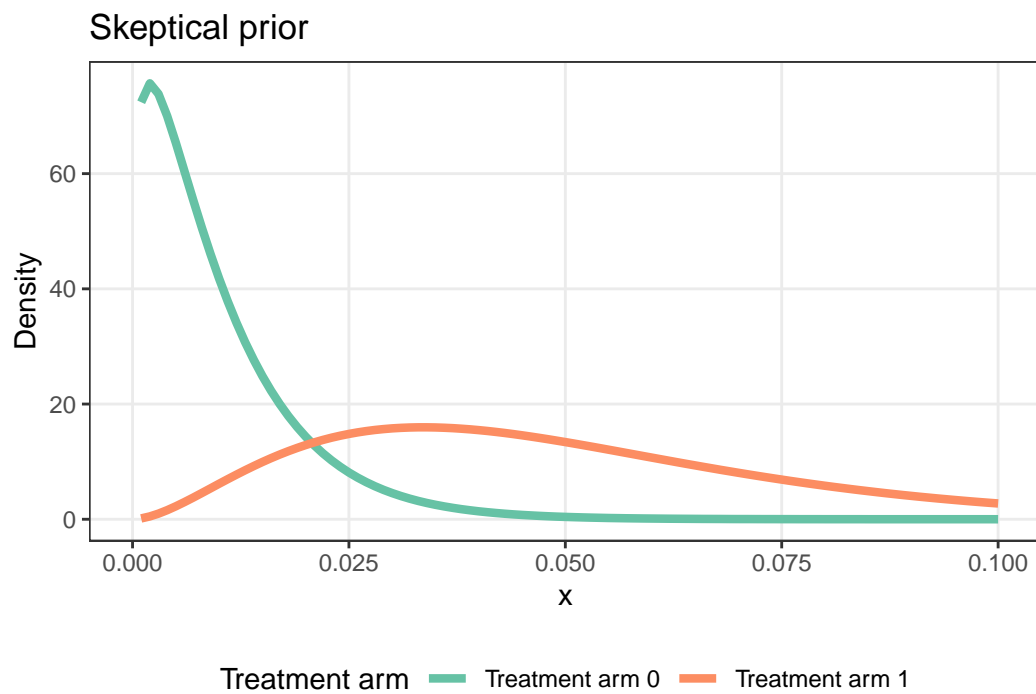
```r
diff_prior <- data.frame(x = rbbinom(1e+06, size = ceiling(n_1), a_1,
    b_1)/ceiling(n_1) - rbbinom(1e+06, size = ceiling(n_0), a_0, b_0)/ceiling(n_0))


fig2 <- ggplot(diff_prior, aes(x)) + geom_density(linewidth = 1.5, bw=0.1) + theme_bw() +
    theme(panel.grid.minor = element_blank()) +
    xlab("Difference from prior predictions") + ggtitle("Simulated distribution of difference f
    ylab("Density") + geom_vline(xintercept=delta_star, linetype="dashed") +
    geom_vline(xintercept=0, linetype="dotted") +
    scale_x_continuous(breaks=c(-0.5, -0.25, 0, 0.035, 0.25, 0.5),
                       labels=c(-0.5, -0.25, 0, 0.035, 0.25, 0.5),
                       limits=c(-0.5, 0.5))


cowplot::plot_grid(fig1, fig2, align = "h", ncol = 1)
```
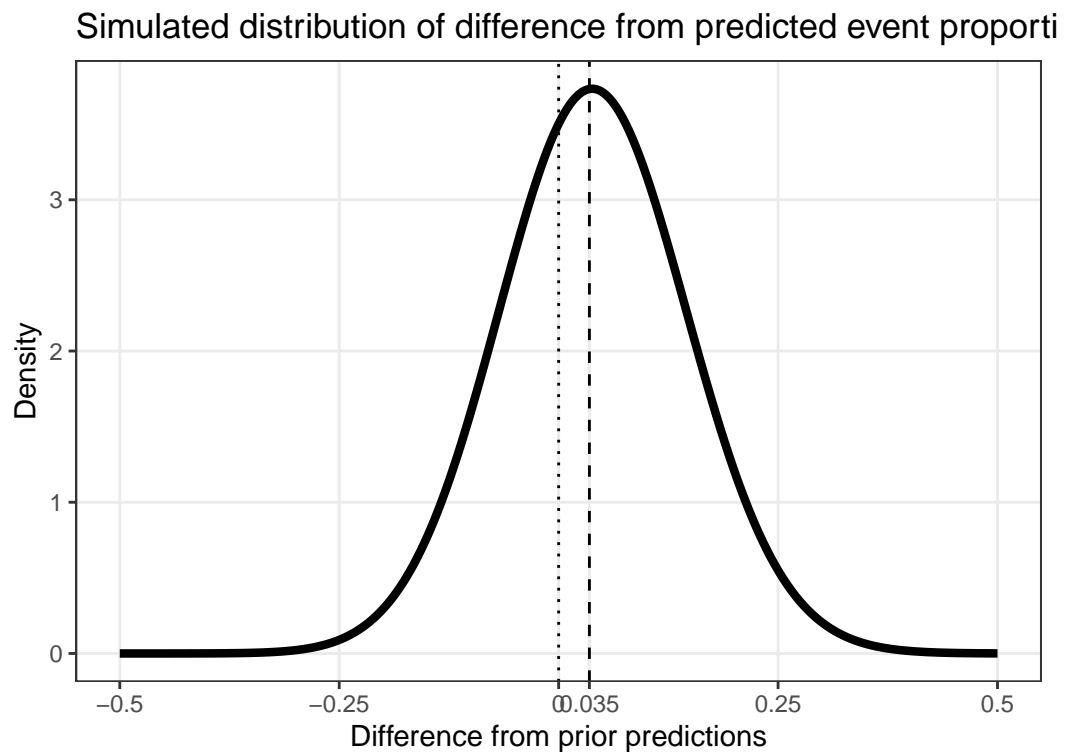
Skeptical prior

Treatment arm — Treatment arm 0 — Treatment arm 1

Assumed event probabilities: Arm 0 (p_0=0.01), Arm 1 (p_1=0.01)

Simulated distribution of difference from predicted event proporti

Informative prior: The beta prior for the active treatment arm and control arm is centered at 0.01 (the

expected event proportion) with $P(\pi_1 \leq 0.05) = 0.01$ and $P(\pi_1 \leq 0.05) = 0.05$.

- Parameters of beta prior for active treatment arm: $a_1 = 0.8$, $b_1 = 79.2$.
- Parameters of beta prior for control treatment arm: $a_0 = 0.03$, $b_0 = 2.97$.

```r
x <- seq(0.001, 0.999, 0.001)


## Informative prior

a_1 <- 0.8

b_1 <- (1 - p_1)/p_1 * a_1

a_0 <- 0.03

b_0 <- (1 - p_0)/p_0 * a_0


prior_0 <- dbeta(x, a_0, b_0)

prior_1 <- dbeta(x, a_1, b_1)




prior_plot <- data.frame(x, prior_0, prior_1)

prior_plot_long <- pivot_longer(prior_plot, cols = c(prior_0, prior_1))


prior_plot_long$group <- ifelse(str_detect(prior_plot_long$name, "_0") ==

    T, "Treatment arm 0", "Treatment arm 1")


fig1 <- ggplot(prior_plot_long, aes(x = x, y = value, colour = group)) +

    geom_line(linewidth = 1.5) + theme_bw() + theme(panel.grid.minor = element_blank(),

    legend.position = "bottom", legend.direction = "horizontal") + scale_x_continuous(limits =

    0.1)) + ylab("Density") + labs(caption = str_glue("Assumed event probabilities: Arm 0 (p_0=

    p_0, "), ", "Arm 1 (p_1=", p_1, ")")) + scale_color_brewer("Treatment arm",

    palette = "Set2") + scale_linetype("Type") + ggtitle("Informative prior")
```
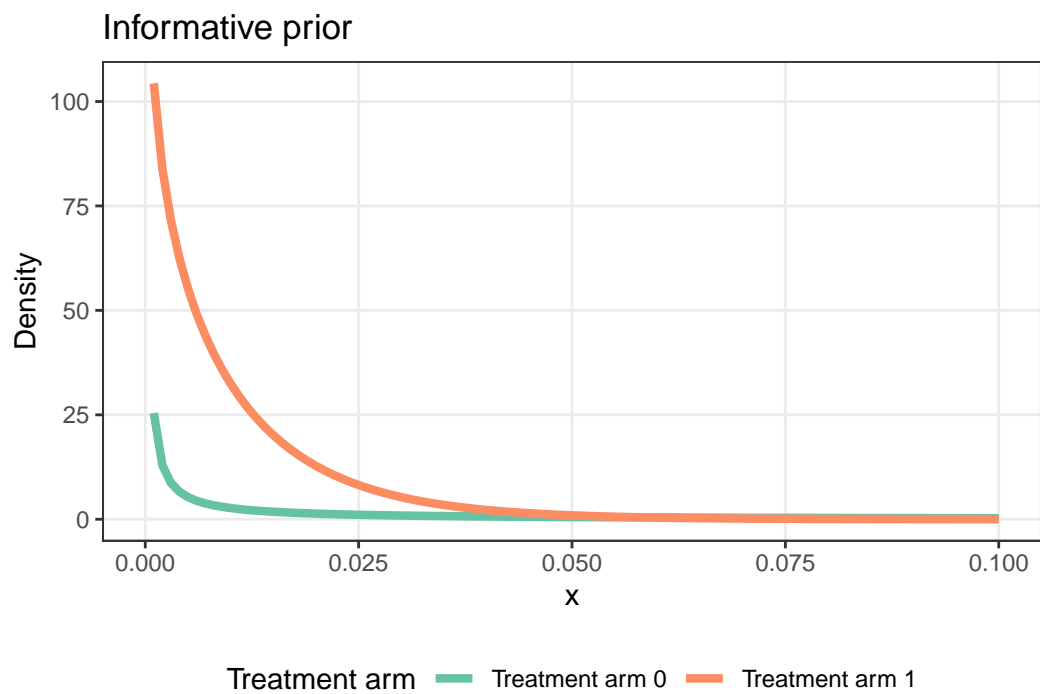
```r
diff_prior <- data.frame(x = rbbinom(1e+06, size = ceiling(n_1), a_1,
    b_1)/ceiling(n_1) - rbbinom(1e+06, size = ceiling(n_0), a_0, b_0)/ceiling(n_0))


fig2 <- ggplot(diff_prior, aes(x)) + geom_density(linewidth = 1.5, bw=0.1) + theme_bw() +
    theme(panel.grid.minor = element_blank()) +
    xlab("Difference from prior predictive distribution") + ggtitle("Simulated distribution of
    ylab("Density") + geom_vline(xintercept=delta_star, linetype="dashed") +
    geom_vline(xintercept=0, linetype="dotted") +
    scale_x_continuous(breaks=c(-0.5, -0.25, 0, 0.035, 0.25, 0.5),
                       labels=c(-0.5, -0.25, 0, 0.035, 0.25, 0.5),
                       limits=c(-0.5, 0.5))


cowplot::plot_grid(fig1, fig2, align = "h", ncol = 1)
```
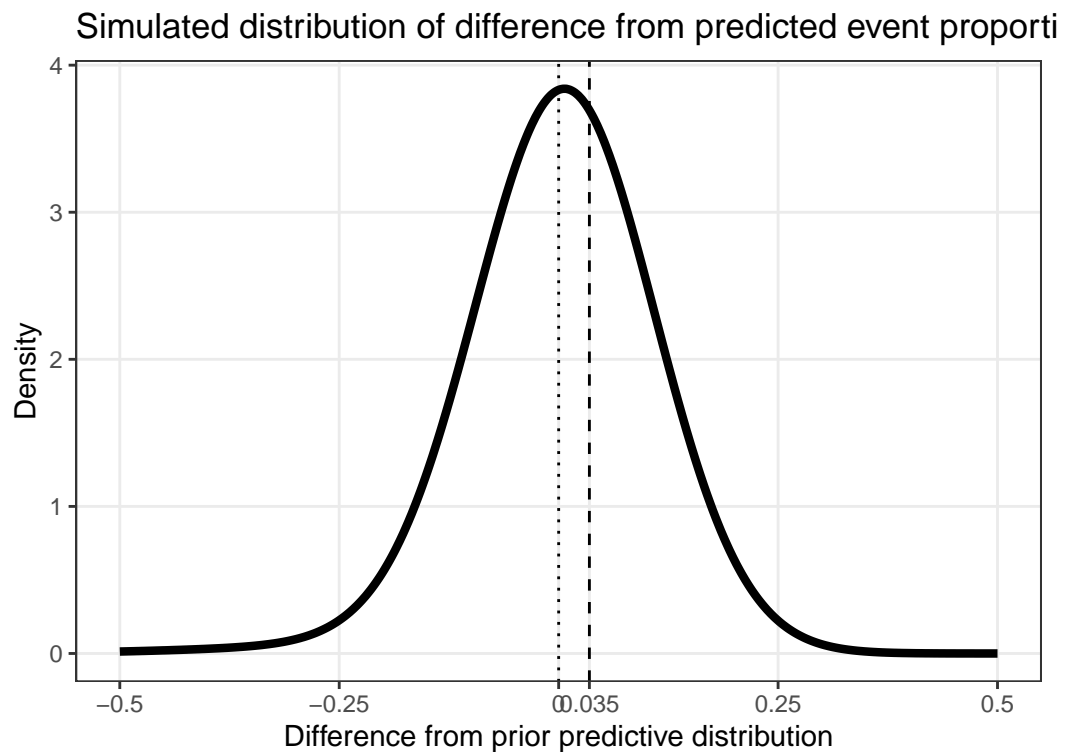
Informative prior

Treatment arm — Treatment arm 0 — Treatment arm 1

Assumed event probabilities: Arm 0 (p_0=0.01), Arm 1 (p_1=0.01)

Simulated distribution of difference from predicted event proporti

Noninformative prior: Uniform prior for both, the active treatment arm and control arm.

- Parameters of beta prior for active treatment arm: $a_1 = 1$, $b_1 = 1$.
- Parameters of beta prior for control treatment arm: $a_0 = 1$, $b_0 = 1$.

```r
## Noninformative prior

a_0 <- 1

b_0 <- 1

a_1 <- 1

b_1 <- 1


prior_0 <- dbeta(x, a_0, b_0)

prior_1 <- dbeta(x, a_1, b_1)


prior_plot <- data.frame(x, prior_0, prior_1)

prior_plot_long <- pivot_longer(prior_plot, cols = c(prior_0, prior_1))


prior_plot_long$group <- ifelse(str_detect(prior_plot_long$name, "_0") ==
    T, "Treatment arm 0", "Treatment arm 1")


fig1 <- ggplot(prior_plot_long, aes(x = x, y = value, colour = group)) +
    geom_line(linewidth = 1.5) + theme_bw() + theme(panel.grid.minor = element_blank(),
    legend.position = "bottom", legend.direction = "horizontal") + scale_x_continuous(limits =
    0.1)) + ylab("Density") + labs(caption = str_glue("Assumed event probabilities: Arm 0 (p_0=
    p_0, "), ", "Arm 1 (p_1=", p_1, ")")) + scale_color_brewer("Treatment arm",
    palette = "Set2") + scale_linetype("Type") + ggtitle("Noninformative prior")


diff_prior <- data.frame(x = rbbinom(1e+06, size = ceiling(n_1), a_1,
    b_1)/ceiling(n_1) - rbbinom(1e+06, size = ceiling(n_0), a_0, b_0)/ceiling(n_0))


fig2 <- ggplot(diff_prior, aes(x)) + geom_density(linewidth = 1.5, bw=0.05) + theme_bw() +
    theme(panel.grid.minor = element_blank()) +
```
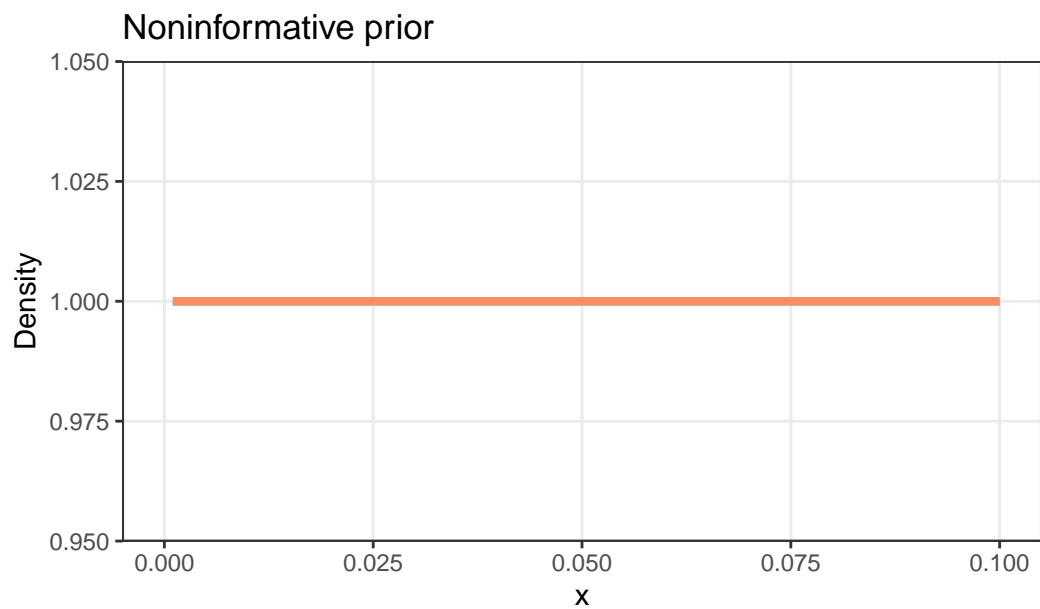
```r
    xlab("Difference from prior predictive distribution") + ggtitle("Simulated distribution of
    ylab("Density") + geom_vline(xintercept=delta_star, linetype="dashed") +
    geom_vline(xintercept=0, linetype="dotted") +
    scale_x_continuous(breaks=c(-1, -0.5, 0, 0.5, 1),
                       labels=c(-1, -0.5, 0,  0.5, 1),
                       limits=c(-1, 1))


cowplot::plot_grid(fig1, fig2, align = "h", ncol = 1)
```

Noninformative prior

Treatment arm — Treatment arm 0 — Treatment arm 1

Assumed event probabilities: Arm 0 (p_0=0.01), Arm 1 (p_1=0.01)

Simulated distribution of difference from predicted event prop
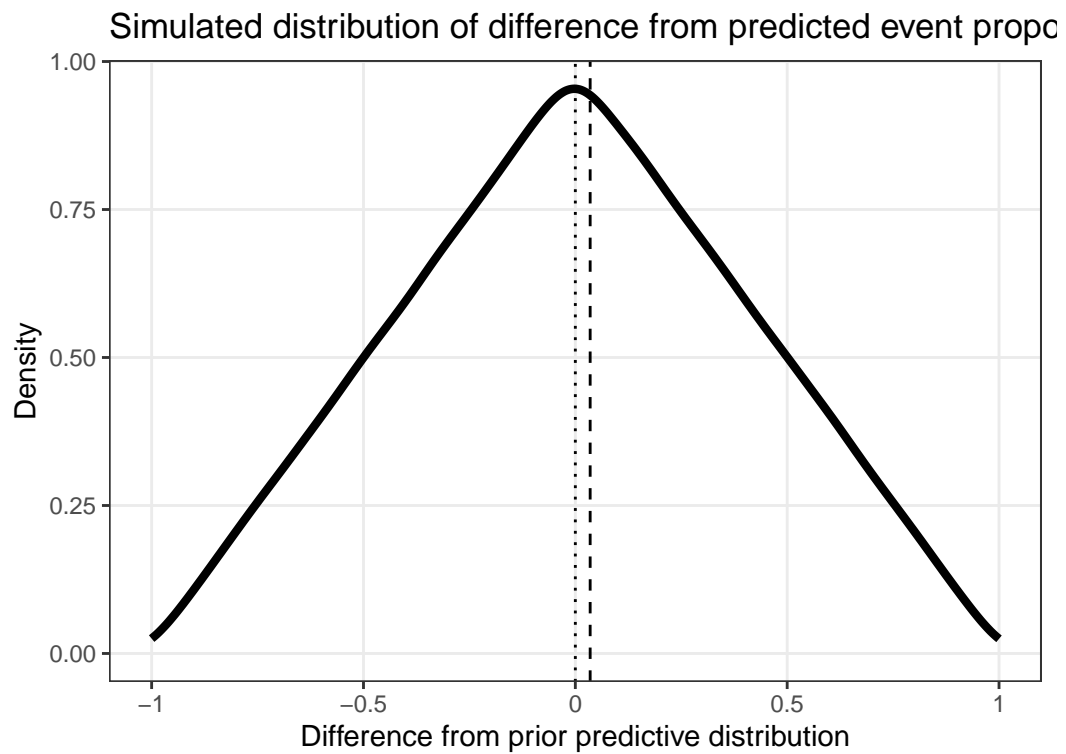
The calculation of the average power is easily done by simulation.

2.2.1.4.1 Simulation approach 1: Joint probability

The joint probability approach has been described in [5] and includes the following steps:

- Calculate the joint pdf for all pairs $r_i \in \{0, 1, \cdots, n_i\}$, $i \in \{0, 1\}$.
- The sum of the joint predictive probabilites over r_i pairs where the $(1 - \alpha)$-upper confidence limit of the risk difference is smaller than the non-inferiority margin is the average power.

Here we use Agresti-Caffo confidence intervals for the risk difference [9].

```r
library(extraDistr)
library(PropCIs)


res_ap <- c()


## Enthusiastic prior


a_1 <- 0.5
b_1 <- (1 - p_1)/p_1 * a_1
a_0 <- 7.2
b_0 <- (1 - 0.03)/0.03 * a_0


r_0 <- 0:(ceiling(n_0)-1)
r_1 <- 0:(ceiling(n_1)-1)


data_points <- expand.grid(r_1 = r_1, r_0 = r_0)


set.seed(1)
data_points$pdf_r_1 <- dbbinom(data_points$r_1, size = ceiling(n_1), a_1,
    b_1)
```

```r
data_points$pdf_r_0 <- dbbinom(data_points$r_0, size = ceiling(n_0), a_0,
    b_0)
data_points$joint_pdf <- data_points$pdf_r_1 * data_points$pdf_r_0


data_points$sig <- NA


for (i in 1:nrow(data_points)) {
    data_points$sig[i] <- ifelse(wald2ci(data_points$r_1[i], n_1, data_points$r_0[i],
        n_0, conf.level = 0.95, adjust = "AC")$conf.int[2] <= delta_star,
        1, 0)
}


res_ap <- data.frame(type = "Enthusiastic",
                          ap = sum(data_points$joint_pdf[data_points$sig == 1]))


## Skeptical prior


a_1 <- 2.84
b_1 <- (1 - 0.05)/0.05 * a_1
a_0 <- 1.24
b_0 <- (1 - 0.01)/0.01 * a_0


r_0 <- 0:(ceiling(n_0)-1)
r_1 <- 0:(ceiling(n_1)-1)


data_points <- expand.grid(r_1 = r_1, r_0 = r_0)


set.seed(1)
data_points$pdf_r_1 <- dbbinom(data_points$r_1, size = ceiling(n_1), a_1,
    b_1)
```

```
data_points$pdf_r_0 <- dbbinom(data_points$r_0, size = ceiling(n_0), a_0,
    b_0)
data_points$joint_pdf <- data_points$pdf_r_1 * data_points$pdf_r_0


data_points$sig <- NA


for (i in 1:nrow(data_points)) {
    data_points$sig[i] <- ifelse(wald2ci(data_points$r_1[i], n_1, data_points$r_0[i],
        n_0, conf.level = 0.95, adjust = "AC")$conf.int[2] <= delta_star,
        1, 0)
}


res_ap <- rbind(res_ap, data.frame(type = "Skeptical",
                        ap = sum(data_points$joint_pdf[data_points$sig == 1])))


## Informative prior


a_1 <- 0.8
b_1 <- (1 - p_1)/p_1 * a_1
a_0 <- 0.03
b_0 <- (1 - p_0)/p_0 * a_0


r_0 <- 0:(ceiling(n_0)-1)
r_1 <- 0:(ceiling(n_1)-1)


data_points <- expand.grid(r_1 = r_1, r_0 = r_0)


set.seed(1)
data_points$pdf_r_1 <- dbbinom(data_points$r_1, size = ceiling(n_1), a_1,
    b_1)
```

```r
data_points$pdf_r_0 <- dbbinom(data_points$r_0, size = ceiling(n_0), a_0,
    b_0)
data_points$joint_pdf <- data_points$pdf_r_1 * data_points$pdf_r_0


data_points$sig <- NA


for (i in 1:nrow(data_points)) {
    data_points$sig[i] <- ifelse(wald2ci(data_points$r_1[i], n_1, data_points$r_0[i],
        n_0, conf.level = 0.95, adjust = "AC")$conf.int[2] <= delta_star,
        1, 0)
}


res_ap <- rbind(res_ap, data.frame(type = "Informative",
                        ap = sum(data_points$joint_pdf[data_points$sig == 1])))


## Noninformative prior


a_1 <- 1
b_1 <- 1
a_0 <- 1
b_0 <- 1


r_0 <- 0:(ceiling(n_0)-1)
r_1 <- 0:(ceiling(n_1)-1)


data_points <- expand.grid(r_1 = r_1, r_0 = r_0)


set.seed(1)
data_points$pdf_r_1 <- dbbinom(data_points$r_1, size = ceiling(n_1), a_1,
    b_1)
```

```r
data_points$pdf_r_0 <- dbbinom(data_points$r_0, size = ceiling(n_0), a_0,
    b_0)
data_points$joint_pdf <- data_points$pdf_r_1 * data_points$pdf_r_0

data_points$sig <- NA

for (i in 1:nrow(data_points)) {
    data_points$sig[i] <- ifelse(wald2ci(data_points$r_1[i], n_1, data_points$r_0[i],
        n_0, conf.level = 0.95, adjust = "AC")$conf.int[2] <= delta_star,
        1, 0)
}

res_ap <- rbind(res_ap, data.frame(type = "Noninformative prior",
                    ap = sum(data_points$joint_pdf[data_points$sig == 1])))
res_ap$ap <- round(res_ap$ap, 2)

res_ap
```

```
                   type   ap
1           Enthusiastic 0.76
2              Skeptical 0.09
3            Informative 0.55
4 Noninformative prior 0.42
```

2.2.1.4.2 Simulation approach 2: Direct sampling from prior predictive distribution

The second simulation approach samples q event outcomes from the predictive distribution and calculates whether the $(1-\alpha)$-upper confidence limit of the risk difference is smaller than the non-inferiority margin. The sum of positive outcomes divided by the number of samples q gives the average power. Also here we use Agresti-Caffo confidence intervals for the risk difference [9].

```r
# Number of draws
q <- 10000


res_ap <- c()


## Enthusiastic prior


a_1 <- 0.5
b_1 <- (1 - p_1)/p_1 * a_1
a_0 <- 7.2
b_0 <- (1 - 0.03)/0.03 * a_0


set.seed(1)
r_1 <- rbbinom(q, size = ceiling(n_1), a_1, b_1)
r_0 <- rbbinom(q, size = ceiling(n_0), a_0, b_0)


res <- c()


for (i in 1:length(r_1)) {
    res <- c(res, ifelse(wald2ci(r_1[i], n_1, r_0[i], n_0, conf.level = 0.95,
        adjust = "AC")$conf.int[2] <= delta_star, 1, 0))
}


res_ap <- data.frame(type = "Enthusiastic", ap = sum(res)/q)


## Skeptical prior


a_1 <- 2.84
b_1 <- (1 - 0.05)/0.05 * a_1
a_0 <- 1.24
```

```r
b_0 <- (1 - p_0)/p_0 * a_0

set.seed(1)
r_1 <- rbbinom(q, size = ceiling(n_1), a_1, b_1)
r_0 <- rbbinom(q, size = ceiling(n_0), a_0, b_0)

res <- c()

for (i in 1:length(r_1)) {
    res <- c(res, ifelse(wald2ci(r_1[i], n_1, r_0[i], n_0, conf.level = 0.95,
        adjust = "AC")$conf.int[2] <= delta_star, 1, 0))
}

res_ap <- rbind(res_ap, data.frame(type = "Skeptical", ap = sum(res)/q))

## Informative prior

a_1 <- 0.8
b_1 <- (1 - p_1)/p_1 * a_1
a_0 <- 0.03
b_0 <- (1 - p_0)/p_0 * a_0

set.seed(1)
r_1 <- rbbinom(q, size = ceiling(n_1), a_1, b_1)
r_0 <- rbbinom(q, size = ceiling(n_0), a_0, b_0)

res <- c()

for (i in 1:length(r_1)) {
    res <- c(res, ifelse(wald2ci(r_1[i], n_1, r_0[i], n_0, conf.level = 0.95,
```

```
                adjust = "AC")$conf.int[2] <= delta_star, 1, 0))
    }


    res_ap <- rbind(res_ap, data.frame(type = "Informative", ap = sum(res)/q))


    ## Noninformative prior


    a_0 <- 1
    b_0 <- 1
    a_1 <- 1
    b_1 <- 1


    set.seed(1)
    r_1 <- rbbinom(q, size = ceiling(n_1), a_1, b_1)
    r_0 <- rbbinom(q, size = ceiling(n_0), a_0, b_0)


    res <- c()


    for (i in 1:length(r_1)) {
        res <- c(res, ifelse(wald2ci(r_1[i], n_1, r_0[i], n_0, conf.level = 0.95,
            adjust = "AC")$conf.int[2] <= delta_star, 1, 0))
    }


    res_ap <- rbind(res_ap, data.frame(type = "Noninformative", ap = sum(res)/q))


    res_ap$ap <- round(res_ap$ap, 2)
    res_ap
```

```
          type   ap
1   Enthusiastic 0.76
```

```
2      Skeptical 0.09

3    Informative 0.55

4 Noninformative 0.42
```

2.2.1.5 Bayesian approach: Prior on event probabilities

In the former subsection we assumed that the prior was directly specified on the treatment effect. In this subsection we assume that that design prior is specified on the event probabilities p_i, $i = \{0, 1\}$. Suppose that the priors on the event probability are beta distributed $\pi_i \sim Beta(a_i, b_i)$, then the posterior distribution is

$$p_i | \pi_i \sim Beta \left(a_i + \sum_{k \leq n_i} Y_{i,k}, b_i + n_i - \sum_{k \leq n_i} Y_{i,k} \right)$$

with

$$\mu_{i,\pi_i} := E(p_i | \pi_i) = \frac{a_i + \sum_{k \leq n_i} Y_{i,k}}{a_i + b_i + n_i}, \quad \sigma^2_{i,\pi_i} := Var(p_i | \pi_i) = \frac{\left(a_i + \sum_{k \leq n_i} Y_{i,k} \right) \left(b_i + n_i - \sum_{k \leq n_i} Y_{i,k} \right)}{(a_i + b_i + n_i)^2 (a_i + b_i + n_i + 1)}.$$

Working example (continued)

We use the same prior specifications as from the former subsection for the analysis priors.

Enthusiastic prior: The beta prior for the active treatment arm is centered at 0.01 (the expected event proportion) with $P(\pi_1 > 0.05) = 0.025$, that is, the probability that the prior is greater than the safety margin is 2.5%. The mean of the beta prior for the control arm is centered at 0.03 (the safety margin) with $P(\pi_0 > 0.05) = 0.05$.

- Parameters of beta prior for active treatment arm: $a_1 = 0.5$, $b_1 = 49.5$.
- Parameters of beta prior for control treatment arm: $a_0 = 7.2$, $b_0 = 232.8$.

```
x <- seq(0.001, 0.999, 0.001)


## Enthusiastic prior
a_1 <- 0.5
```
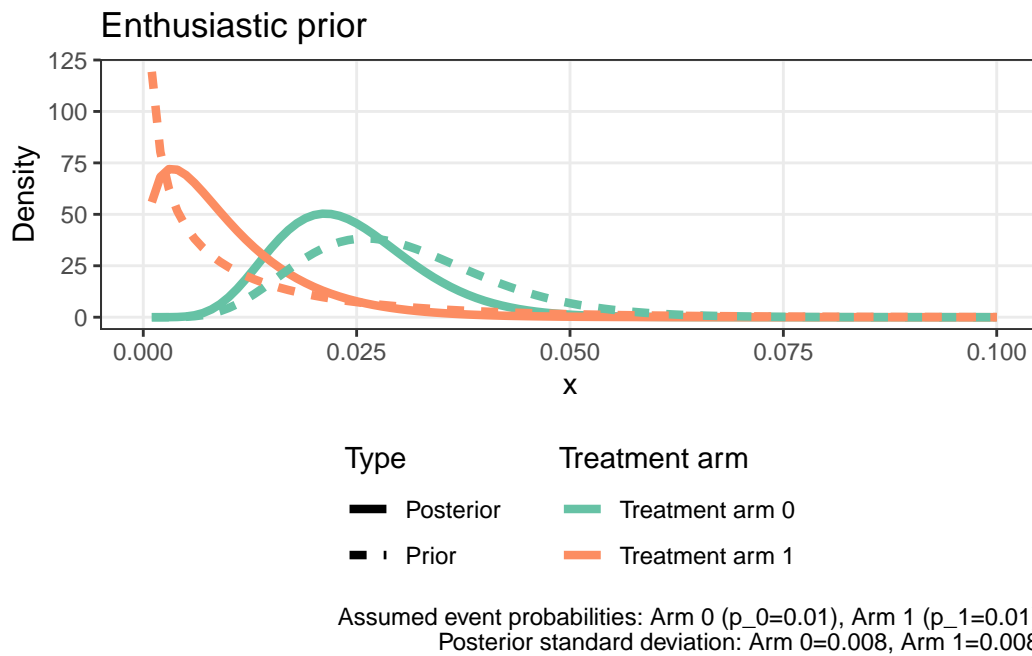
```r
b_1 <- (1 - p_1)/p_1 * a_1
a_0 <- 7.2
b_0 <- (1 - 0.03)/0.03 * a_0


prior_0 <- dbeta(x, a_0, b_0)
prior_1 <- dbeta(x, a_1, b_1)
posterior_0 <- dbeta(x, a_0 + n_0 * p_0, b_0 + n_0 - n_0 * p_0)
posterior_1 <- dbeta(x, a_1 + n_1 * p_1, b_1 + n_1 - n_1 * p_1)
var_posterior_0 <- ((a_0 + n_0 * p_0) * (b_0 + n_0 - n_0 * p_0))/((a_0 +
    b_0 + n_0)^2 * (a_0 + b_0 + n_0 + 1))
var_posterior_1 <- ((a_1 + n_1 * p_1) * (b_1 + n_1 - n_1 * p_1))/((a_1 +
    b_1 + n_1)^2 * (a_1 + b_1 + n_1 + 1))


prior_plot <- data.frame(x, prior_0, prior_1, posterior_0, posterior_1)
prior_plot_long <- pivot_longer(prior_plot, cols = c(prior_0, prior_1,
    posterior_0, posterior_1))
prior_plot_long$type <- ifelse(str_detect(prior_plot_long$name, "posterior") ==
    T, "Posterior", "Prior")
prior_plot_long$group <- ifelse(str_detect(prior_plot_long$name, "_0") ==
    T, "Treatment arm 0", "Treatment arm 1")


ggplot(prior_plot_long, aes(x = x, y = value, linetype = type, colour = group)) +
    geom_line(linewidth = 1.5) + theme_bw() + theme(panel.grid.minor = element_blank(),
    legend.position = "bottom", legend.direction = "vertical") + scale_x_continuous(limits = c(
    0.1)) + ylab("Density") + labs(caption = str_glue("Assumed event probabilities: Arm 0 (p_0=
    p_0, "), ", "Arm 1 (p_1=", p_1, ")\nPosterior standard deviation: Arm 0=",
    round(sqrt(var_posterior_0), 3), ", ", "Arm 1=", round(sqrt(var_posterior_1),
        3))) + scale_color_brewer("Treatment arm", palette = "Set2") +
    scale_linetype("Type") + ggtitle("Enthusiastic prior")
```

Enthusiastic prior

Assumed event probabilities: Arm 0 (p_0=0.01), Arm 1 (p_1=0.01)
Posterior standard deviation: Arm 0=0.008, Arm 1=0.008

Skeptical prior: The beta prior for the active treatment arm is centered at 0.05 (the safety margin) with $P(\pi_1 \leq 0.01) = 0.025$, that is the probability that the prior is smaller or equal than the expected event proportion is 2.5%. The mean of the beta prior for the control arm is is centered at 0.01 (the expected event proportion) with $P(\pi_0 > 0.05) = 0.025$.

- Parameters of beta prior for active treatment arm: $a_1 = 2.84$, $b_1 = 53.96$.
- Parameters of beta prior for control treatment arm: $a_i = 1.24$, $b_i = 122.76$.

```
x <- seq(0.001, 0.999, 0.001)


# Skeptical
a_1 <- 2.84
b_1 <- (1 - 0.05)/0.05 * a_1
a_0 <- 1.24
b_0 <- (1 - p_0)/p_0 * a_0


prior_0 <- dbeta(x, a_0, b_0)
```
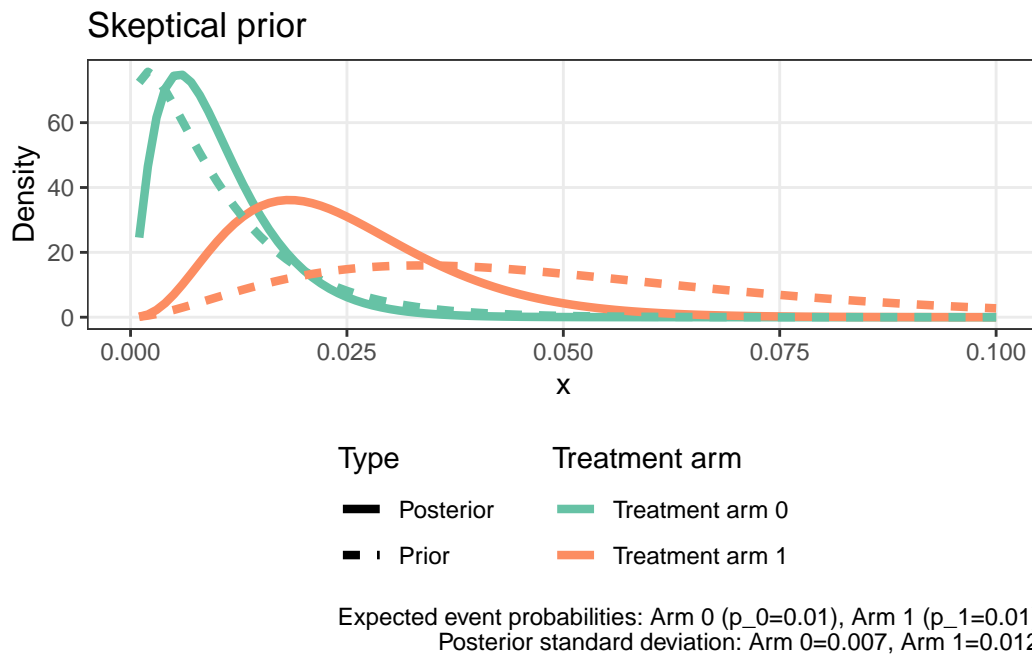
```r
prior_1 <- dbeta(x, a_1, b_1)
posterior_0 <- dbeta(x, a_0 + n_0 * p_0, b_0 + n_0 - n_0 * p_0)
posterior_1 <- dbeta(x, a_1 + n_1 * p_1, b_1 + n_1 - n_1 * p_1)
var_posterior_0 <- ((a_0 + n_0 * p_0) * (b_0 + n_0 - n_0 * p_0))/((a_0 +
    b_0 + n_0)^2 * (a_0 + b_0 + n_0 + 1))
var_posterior_1 <- ((a_1 + n_1 * p_1) * (b_1 + n_1 - n_1 * p_1))/((a_1 +
    b_1 + n_1)^2 * (a_1 + b_1 + n_1 + 1))


prior_plot <- data.frame(x, prior_0, prior_1, posterior_0, posterior_1)
prior_plot_long <- pivot_longer(prior_plot, cols = c(prior_0, prior_1,
    posterior_0, posterior_1))
prior_plot_long$type <- ifelse(str_detect(prior_plot_long$name, "posterior") ==
    T, "Posterior", "Prior")
prior_plot_long$group <- ifelse(str_detect(prior_plot_long$name, "_0") ==
    T, "Treatment arm 0", "Treatment arm 1")


ggplot(prior_plot_long, aes(x = x, y = value, linetype = type, colour = group)) +
    geom_line(linewidth = 1.5) + theme_bw() + theme(panel.grid.minor = element_blank(),
    legend.position = "bottom", legend.direction = "vertical") + scale_x_continuous(limits = c(
    0.1)) + ylab("Density") + labs(caption = str_glue("Expected event probabilities: Arm 0 (p_0
    p_0, "), ", "Arm 1 (p_1=", p_1, ")\nPosterior standard deviation: Arm 0=",
    round(sqrt(var_posterior_0), 3), ", ", "Arm 1=", round(sqrt(var_posterior_1),
        3))) + scale_color_brewer("Treatment arm", palette = "Set2") +
    scale_linetype("Type") + ggtitle("Skeptical prior")
```

Skeptical prior

Expected event probabilities: Arm 0 (p_0=0.01), Arm 1 (p_1=0.01)
Posterior standard deviation: Arm 0=0.007, Arm 1=0.012

Informative prior: The beta prior for the active treatment arm and control arm is centered at 0.01 (the expected event proportion) with $P(\pi_1 \leq 0.05) = 0.01$ and $P(\pi_1 \leq 0.05) = 0.05$.

- Parameters of beta prior for active treatment arm: $a_1 = 0.8$, $b_1 = 79.2$.
- Parameters of beta prior for control treatment arm: $a_0 = 0.03$, $b_0 = 2.97$.

```r
x <- seq(0.001, 0.999, 0.001)


## Enthusiastic
a_1 <- 0.8
b_1 <- (1 - p_1)/p_1 * a_1
a_0 <- 0.03
b_0 <- (1 - p_0)/p_0 * a_0


prior_0 <- dbeta(x, a_0, b_0)
prior_1 <- dbeta(x, a_1, b_1)
posterior_0 <- dbeta(x, a_0 + n_0 * p_0, b_0 + n_0 - n_0 * p_0)
```
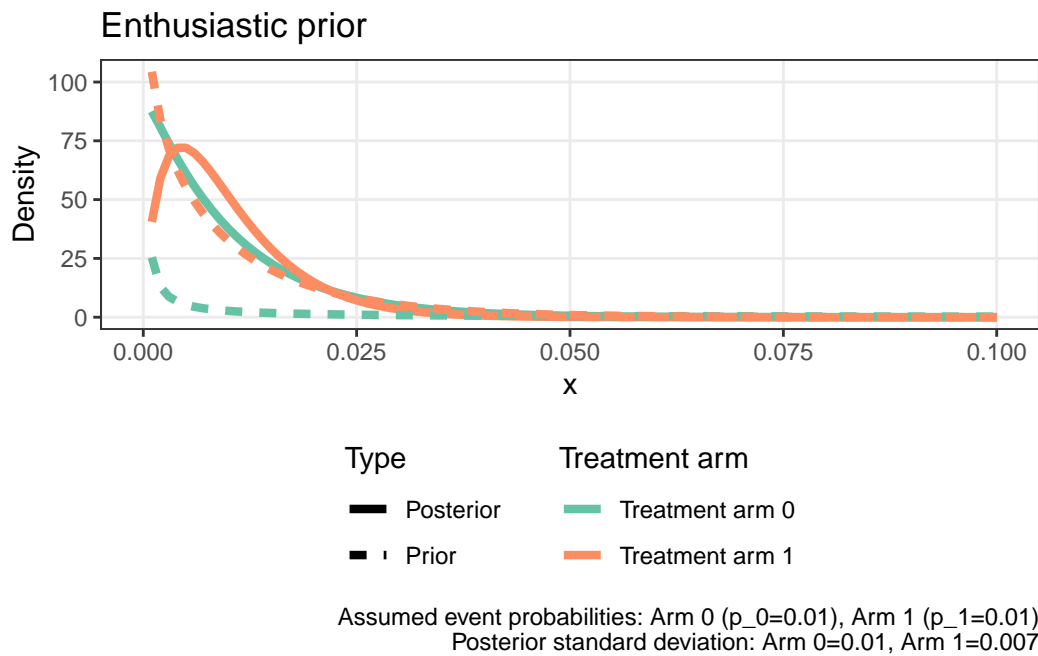
```r
posterior_1 <- dbeta(x, a_1 + n_1 * p_1, b_1 + n_1 - n_1 * p_1)
var_posterior_0 <- ((a_0 + n_0 * p_0) * (b_0 + n_0 - n_0 * p_0))/((a_0 +
    b_0 + n_0)^2 * (a_0 + b_0 + n_0 + 1))
var_posterior_1 <- ((a_1 + n_1 * p_1) * (b_1 + n_1 - n_1 * p_1))/((a_1 +
    b_1 + n_1)^2 * (a_1 + b_1 + n_1 + 1))


prior_plot <- data.frame(x, prior_0, prior_1, posterior_0, posterior_1)
prior_plot_long <- pivot_longer(prior_plot, cols = c(prior_0, prior_1,
    posterior_0, posterior_1))
prior_plot_long$type <- ifelse(str_detect(prior_plot_long$name, "posterior") ==
    T, "Posterior", "Prior")
prior_plot_long$group <- ifelse(str_detect(prior_plot_long$name, "_0") ==
    T, "Treatment arm 0", "Treatment arm 1")


ggplot(prior_plot_long, aes(x = x, y = value, linetype = type, colour = group)) +
    geom_line(linewidth = 1.5) + theme_bw() + theme(panel.grid.minor = element_blank(),
    legend.position = "bottom", legend.direction = "vertical") + scale_x_continuous(limits = c(
    0.1)) + ylab("Density") + labs(caption = str_glue("Assumed event probabilities: Arm 0 (p_0=
    p_0, "), ", "Arm 1 (p_1=", p_1, ")\nPosterior standard deviation: Arm 0=",
    round(sqrt(var_posterior_0), 3), ", ", "Arm 1=", round(sqrt(var_posterior_1),
        3))) + scale_color_brewer("Treatment arm", palette = "Set2") +
    scale_linetype("Type") + ggtitle("Enthusiastic prior")
```

Enthusiastic prior

Assumed event probabilities: Arm 0 (p_0=0.01), Arm 1 (p_1=0.01)
Posterior standard deviation: Arm 0=0.01, Arm 1=0.007

Noninformative prior: Uniform prior for both, the active treatment arm and control arm.

- Parameters of beta prior for active treatment arm: $a_1 = 1$, $b_1 = 1$.

- Parameters of beta prior for control treatment arm: $a_0 = 1$, $b_0 = 1$.

```
## Uniform
a_0 <- 1
b_0 <- 1
a_1 <- 1
b_1 <- 1


prior_0 <- dbeta(x, a_0, b_0)
prior_1 <- dbeta(x, a_1, b_1)
posterior_0 <- dbeta(x, a_0 + n_0 * p_0, b_0 + n_0 -
    n_0 * p_0)
posterior_1 <- dbeta(x, a_1 + n_1 * p_1, b_1 + n_1 -
    n_1 * p_1)
```

```r
var_posterior_0 <- ((a_0 + n_0 * p_0) * (b_0 + n_0 -
    n_0 * p_0))/((a_0 + b_0 + n_0)^2 * (a_0 + b_0 +
    n_0 + 1))
var_posterior_1 <- ((a_1 + n_1 * p_1) * (b_1 + n_1 -
    n_1 * p_1))/((a_1 + b_1 + n_1)^2 * (a_1 + b_1 +
    n_1 + 1))


prior_plot <- data.frame(x, prior_0, prior_1, posterior_0,
    posterior_1)
prior_plot_long <- pivot_longer(prior_plot, cols = c(prior_0,
    prior_1, posterior_0, posterior_1))
prior_plot_long$type <- ifelse(str_detect(prior_plot_long$name,
    "posterior") == T, "Posterior", "Prior")
prior_plot_long$group <- ifelse(str_detect(prior_plot_long$name,
    "_0") == T, "Treatment arm 0", "Treatment arm 1")


ggplot(prior_plot_long, aes(x = x, y = value, linetype = type,
    colour = group)) + geom_line(linewidth = 1.5) +
    theme_bw() + theme(panel.grid.minor = element_blank(),
    legend.position = "bottom", legend.direction = "vertical") +
    scale_x_continuous(limits = c(0, 0.1)) + ylab("Density") +
    labs(caption = str_glue("Assumed event probabilities: Arm 0 (p_0=",
        p_0, "), ", "Arm 1 (p_1=", p_1, ")\nPosterior standard deviation: Arm 0=",
        round(sqrt(var_posterior_0), 3), ", ", "Arm 1=",
        round(sqrt(var_posterior_1), 3))) + scale_color_brewer("Treatment arm",
    palette = "Set2") + scale_linetype("Type") + ggtitle("Noninformative prior")
```

Noninformative prior

Assumed event probabilities: Arm 0 (p_0=0.01), Arm 1 (p_1=0.01)
Posterior standard deviation: Arm 0=0.014, Arm 1=0.014
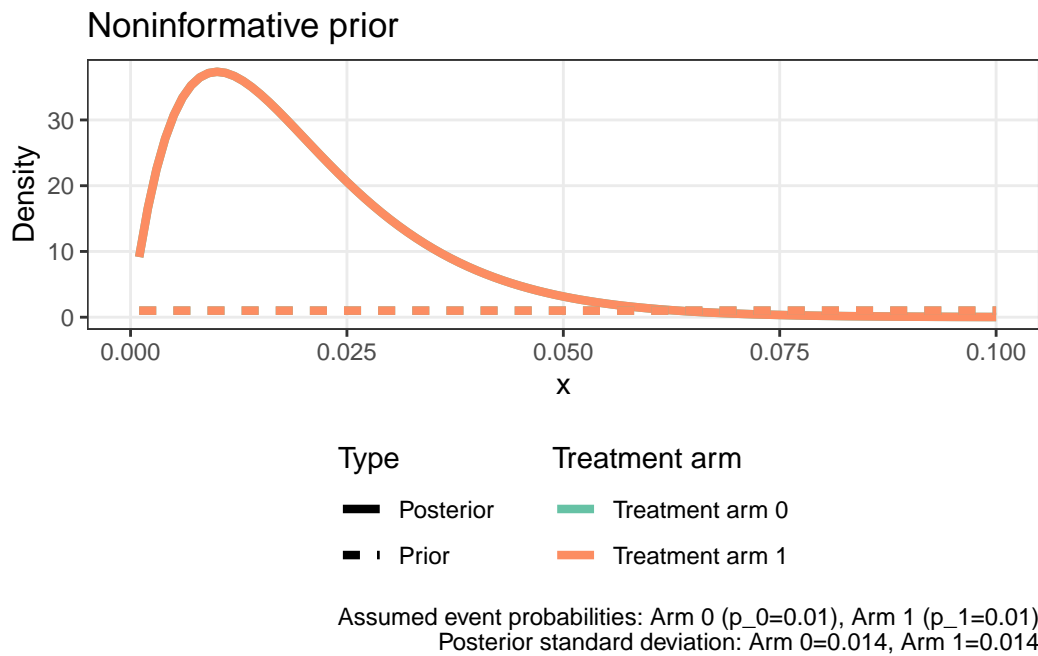
The calculation of the Bayesian average power is again done by simulation.

```
# Number of draws

q <- 10000


## Enthusiastic prior


a_1 <- 0.5
b_1 <- (1 - p_1)/p_1 * a_1
a_0 <- 7.2
b_0 <- (1 - 0.03)/0.03 * a_0


m <- 100
set.seed(1)
r_1 <- rbbinom(q, size = m, a_1 + ceiling(n_1) * p_1,
```

```r
    b_1 + ceiling(n_1) - ceiling(n_1) * p_1)
mean_r_1 <- m * (a_1 + ceiling(n_1) * p_1)/(a_1 + ceiling(n_1) *
    p_1 + b_1 + ceiling(n_1) - ceiling(n_1) * p_1)
var_posterior_1 <- (m * (a_1 + ceiling(n_1) * p_1) *
    (b_1 + ceiling(n_1) - ceiling(n_1) * p_1) * (m +
    a_1 + ceiling(n_1) * p_1 + b_1 + ceiling(n_1) -
    ceiling(n_1) * p_1))/((a_1 + ceiling(n_1) * p_1 +
    b_1 + ceiling(n_1) - ceiling(n_1) * p_1)^2 * (a_1 +
    ceiling(n_1) * p_1 + b_1 + ceiling(n_1) - ceiling(n_1) *
    p_1 + 1))


r_0 <- rbbinom(q, size = m, a_0 + ceiling(n_0) * p_0,
    b_0 + ceiling(n_0) - ceiling(n_0) * p_0)
mean_r_0 <- m * (a_0 + ceiling(n_0) * p_0)/(a_0 + ceiling(n_0) *
    p_0 + b_0 + ceiling(n_0) - ceiling(n_0) * p_0)
var_posterior_0 <- (m * (a_0 + ceiling(n_0) * p_0) *
    (b_0 + ceiling(n_0) - ceiling(n_0) * p_0) * (m +
    a_0 + ceiling(n_0) * p_0 + b_0 + ceiling(n_0) -
    ceiling(n_0) * p_0))/((a_0 + ceiling(n_0) * p_0 +
    b_0 + ceiling(n_0) - ceiling(n_0) * p_0)^2 * (a_0 +
    ceiling(n_0) * p_0 + b_0 + ceiling(n_0) - ceiling(n_0) *
    p_0 + 1))


data_bap <- data.frame(pred_1 = r_1/m, pred_0 = r_0/m,
    diff = r_1/m - r_0/m, type = "Enthusiastic")


data_bap_graph <- data_bap


bap <- sum(ifelse(data_bap$diff + qnorm(1 - alpha) *
    sqrt(var_posterior_0 + var_posterior_1)/m <= delta_star,
```

```
      1, 0))/q


res_bap <- data.frame(type = "Enthusiastic", bap = bap)


## Skeptical prior


a_1 <- 2.84

b_1 <- (1 - 0.05)/0.05 * a_1

a_0 <- 1.24

b_0 <- (1 - p_0)/p_0 * a_0


m <- 100

set.seed(1)

r_1 <- rbbinom(q, size = m, a_1 + ceiling(n_1) * p_1,

    b_1 + ceiling(n_1) - ceiling(n_1) * p_1)

mean_r_1 <- m * (a_1 + ceiling(n_1) * p_1)/(a_1 + ceiling(n_1) *

    p_1 + b_1 + ceiling(n_1) - ceiling(n_1) * p_1)

var_posterior_1 <- (m * (a_1 + ceiling(n_1) * p_1) *

    (b_1 + ceiling(n_1) - ceiling(n_1) * p_1) * (m +

    a_1 + ceiling(n_1) * p_1 + b_1 + ceiling(n_1) -

    ceiling(n_1) * p_1))/((a_1 + ceiling(n_1) * p_1 +

    b_1 + ceiling(n_1) - ceiling(n_1) * p_1)^2 * (a_1 +

    ceiling(n_1) * p_1 + b_1 + ceiling(n_1) - ceiling(n_1) *

    p_1 + 1))


r_0 <- rbbinom(q, size = m, a_0 + ceiling(n_0) * p_0,

    b_0 + ceiling(n_0) - ceiling(n_0) * p_0)

mean_r_0 <- m * (a_0 + ceiling(n_0) * p_0)/(a_0 + ceiling(n_0) *

    p_0 + b_0 + ceiling(n_0) - ceiling(n_0) * p_0)

var_posterior_0 <- (m * (a_0 + ceiling(n_0) * p_0) *
```

```r
    (b_0 + ceiling(n_0) - ceiling(n_0) * p_0) * (m +
        a_0 + ceiling(n_0) * p_0 + b_0 + ceiling(n_0) -
        ceiling(n_0) * p_0))/((a_0 + ceiling(n_0) * p_0 +
        b_0 + ceiling(n_0) - ceiling(n_0) * p_0)^2 * (a_0 +
        ceiling(n_0) * p_0 + b_0 + ceiling(n_0) - ceiling(n_0) *
        p_0 + 1))


data_bap <- data.frame(pred_1 = r_1/m,
    pred_0 = r_0/m, diff = r_1/m - r_0/m, type = "Skeptical")


data_bap_graph <- rbind(data_bap_graph, data_bap)


bap <- sum(ifelse(data_bap$diff + qnorm(1 - alpha) *
    sqrt(var_posterior_0 + var_posterior_1)/m <= delta_star,
    1, 0))/q


res_bap <- rbind(res_bap, data.frame(type = "Skeptical",
    bap = bap))


## Informative prior


a_1 <- 0.8
b_1 <- (1 - p_1)/p_1 * a_1
a_0 <- 0.03
b_0 <- (1 - p_0)/p_0 * a_0


m <- 100
set.seed(1)
r_1 <- rbbinom(q, size = m, a_1 + ceiling(n_1) * p_1,
    b_1 + ceiling(n_1) - ceiling(n_1) * p_1)
```

```
mean_r_1 <- m * (a_1 + ceiling(n_1) * p_1)/(a_1 + ceiling(n_1) *
    p_1 + b_1 + ceiling(n_1) - ceiling(n_1) * p_1)
var_posterior_1 <- (m * (a_1 + ceiling(n_1) * p_1) *
    (b_1 + ceiling(n_1) - ceiling(n_1) * p_1) * (m +
    a_1 + ceiling(n_1) * p_1 + b_1 + ceiling(n_1) -
    ceiling(n_1) * p_1))/((a_1 + ceiling(n_1) * p_1 +
    b_1 + ceiling(n_1) - ceiling(n_1) * p_1)^2 * (a_1 +
    ceiling(n_1) * p_1 + b_1 + ceiling(n_1) - ceiling(n_1) *
    p_1 + 1))

r_0 <- rbbinom(q, size = m, a_0 + ceiling(n_0) * p_0,
    b_0 + ceiling(n_0) - ceiling(n_0) * p_0)
mean_r_0 <- m * (a_0 + ceiling(n_0) * p_0)/(a_0 + ceiling(n_0) *
    p_0 + b_0 + ceiling(n_0) - ceiling(n_0) * p_0)
var_posterior_0 <- (m * (a_0 + ceiling(n_0) * p_0) *
    (b_0 + ceiling(n_0) - ceiling(n_0) * p_0) * (m +
    a_0 + ceiling(n_0) * p_0 + b_0 + ceiling(n_0) -
    ceiling(n_0) * p_0))/((a_0 + ceiling(n_0) * p_0 +
    b_0 + ceiling(n_0) - ceiling(n_0) * p_0)^2 * (a_0 +
    ceiling(n_0) * p_0 + b_0 + ceiling(n_0) - ceiling(n_0) *
    p_0 + 1))

data_bap <- data.frame(pred_1 = r_1/m,
    pred_0 = r_0/m, diff = r_1/m - r_0/m, type = "Informative")

data_bap_graph <- rbind(data_bap_graph, data_bap)

bap <- sum(ifelse(data_bap$diff + qnorm(1 - alpha) *
    sqrt(var_posterior_0 + var_posterior_1)/m <= delta_star,
    1, 0))/q
```

```r
res_bap <- rbind(res_bap, data.frame(type = "Informative",
    bap = bap))


## Noninformative prior

a_0 <- 1
b_0 <- 1
a_1 <- 1
b_1 <- 1


m <- 100
set.seed(1)
r_1 <- rbbinom(q, size = m, a_1 + ceiling(n_1) * p_1,
    b_1 + ceiling(n_1) - ceiling(n_1) * p_1)
mean_r_1 <- m * (a_1 + ceiling(n_1) * p_1)/(a_1 + ceiling(n_1) *
    p_1 + b_1 + ceiling(n_1) - ceiling(n_1) * p_1)
var_posterior_1 <- (m * (a_1 + ceiling(n_1) * p_1) *
    (b_1 + ceiling(n_1) - ceiling(n_1) * p_1) * (m +
    a_1 + ceiling(n_1) * p_1 + b_1 + ceiling(n_1) -
    ceiling(n_1) * p_1))/((a_1 + ceiling(n_1) * p_1 +
    b_1 + ceiling(n_1) - ceiling(n_1) * p_1)^2 * (a_1 +
    ceiling(n_1) * p_1 + b_1 + ceiling(n_1) - ceiling(n_1) *
    p_1 + 1))


r_0 <- rbbinom(q, size = m, a_0 + ceiling(n_0) * p_0,
    b_0 + ceiling(n_0) - ceiling(n_0) * p_0)
mean_r_0 <- m * (a_0 + ceiling(n_0) * p_0)/(a_0 + ceiling(n_0) *
    p_0 + b_0 + ceiling(n_0) - ceiling(n_0) * p_0)
var_posterior_0 <- (m * (a_0 + ceiling(n_0) * p_0) *
```

```
        (b_0 + ceiling(n_0) - ceiling(n_0) * p_0) * (m +

        a_0 + ceiling(n_0) * p_0 + b_0 + ceiling(n_0) -

        ceiling(n_0) * p_0))/((a_0 + ceiling(n_0) * p_0 +

        b_0 + ceiling(n_0) - ceiling(n_0) * p_0)^2 * (a_0 +

        ceiling(n_0) * p_0 + b_0 + ceiling(n_0) - ceiling(n_0) *

        p_0 + 1))


    data_bap <- data.frame(pred_1 = r_1/m,

        pred_0 = r_0/m, diff = r_1/m - r_0/m, type = "Noninformative")


    data_bap_graph <- rbind(data_bap_graph, data_bap)


    bap <- sum(ifelse(data_bap$diff + qnorm(1 - alpha) *

        sqrt(var_posterior_0 + var_posterior_1)/m <= delta_star,

        1, 0))/q


    res_bap <- rbind(res_bap, data.frame(type = "Noninformative",

        bap = bap))


    res_bap$bap <- round(res_bap$bap, 2)

    res_bap
```

```
            type  bap
1    Enthusiastic 0.68
2       Skeptical 0.18
3     Informative 0.64
4 Noninformative 0.25
```

```
    ggplot(data_bap_graph, aes(x = pred_1 - pred_0)) + geom_density(linewidth = 1.5,

        bw = 0.01) + facet_wrap(~type) + geom_vline(xintercept = delta_star,
```

```
linetype = "dashed") + theme_bw() + theme(panel.grid.minor = element_blank()) +

geom_vline(xintercept = 0, linetype = "dotted") +

xlab("Difference in posterior predicted event proportions") +

ylab("Density") + scale_x_continuous(breaks = c(-0.1,

0, 0.035, 0.1), labels = c(-0.1, 0, 0.035, 0.1)) +

ggtitle("Difference in posterior predicted event proportions")
```

Difference in posterior predicted event proportions

Difference in posterior predicted event proportions
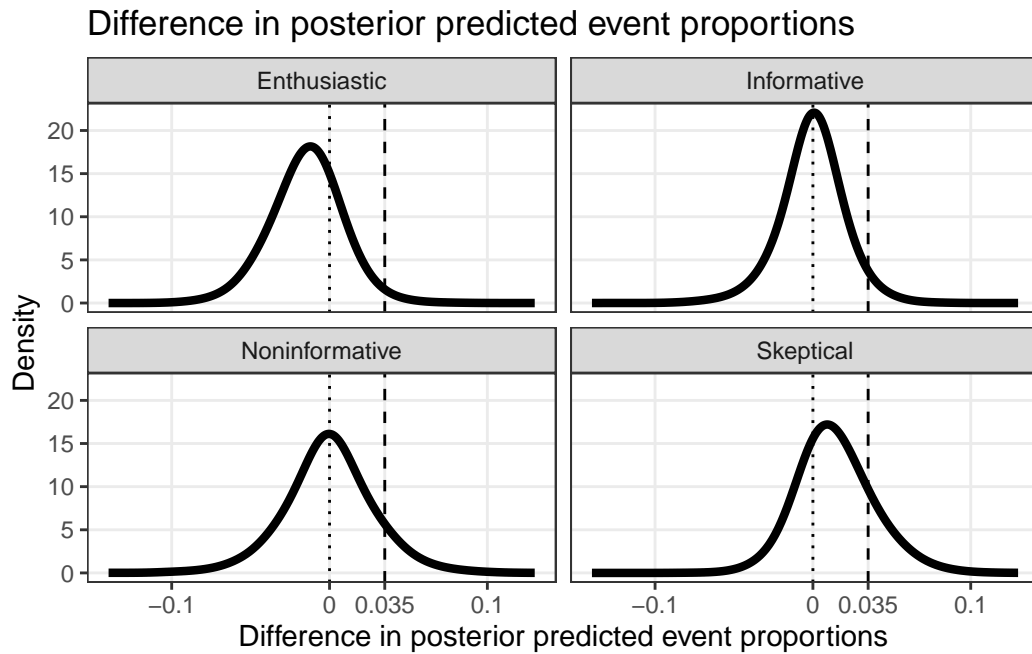
References

1. Kunzmann K, Grayling MJ, Lee KM, Robertson DS, Rufibach K, Wason JMS. A review of bayesian perspectives on sample size derivation for confirmatory trials. The American Statistician. 2021;75: 424–432. doi:10.1080/00031305.2021.1901782

2. Stefan AM, Gronau QF, Schönbrodt FD, Wagenmakers E-J. A tutorial on bayes factor design analysis using an informed prior. Behavior Research Methods. 2019;51: 1042–1058. doi:10.3758/s13428-018-01189-8

3. Spiegelhalter DJ, Abrams KR, Myles JP. Bayesian approaches to clinical trials and health-care evaluation. Wiley; 2003. doi:10.1002/0470092602

4. Baumgartner C, Klok FA, Carrier M, Limacher A, Moor J, Righini M, et al. Clinical surveillance vs. Anticoagulation for low-risk patiEnts with isolated SubSegmental pulmonary embolism: Protocol for a multicentre randomised placebo-controlled non-inferiority trial (SAFE-SSPE). BMJ Open. 2020;10: e040151. doi:10.1136/bmjopen-2020-040151

5. Grieve AP. Hybrid frequentist/bayesian power and bayesian power in planning clinical trials. Chapman; Hall/CRC; 2022. doi:10.1201/9781003218531

6. O'Hagan A, Stevens JW, Campbell MJ. Assurance in clinical trial design. Pharmaceutical Statistics. 2005;4: 187–201. doi:10.1002/pst.175

7. Rufibach K, Burger HU, Abt M. Bayesian predictive power: Choice of prior and some recommendations for its use as probability of success in drug development. Pharmaceutical Statistics. 2016;15: 438–446. doi:10.1002/pst.1764

8. Gelman A, Carlin JB, Stern HS, Dunson DB, Vehtari A, Rubin DB. Bayesian data analysis. Chapman; Hall/CRC; 2013. doi:10.1201/b16018

9. Agresti A, Caffo B. Simple and effective confidence intervals for proportions and differences of proportions result from adding two successes and two failures. The American Statistician. 2000;54: 280. doi:10.2307/2685779