

# Expected Power for the TOST Procedure

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The following elaboration is based on [1], [2], [4] and [5].

## 1 Motivation

For some fixed  $\theta_0 \in \mathbb{R}$ ,  $\sigma^2 \in \mathbb{R}_{>0}$ , let  $\pi$  denote the power function  $\pi(\theta_0, \sigma^2) = \mathbb{P}(R | \theta_0, \sigma^2)$ , where the event  $R$  denotes the rejection of the null hypothesis of non-equivalence. We assume that the parameters are specified on the additive scale. The function  $\pi = \pi(\theta_0, \sigma^2)$  is the same as in equation (I) in the short cursory excerpt on BE within inst/doc/.

This power function is conditional on the unknown (true) values  $\theta_0$  and  $\sigma^2$ . That is, it is assumed that those parameters are given as known entities. Therefore, this probability only reflects the probability of trial success if  $\theta_0$  and  $\sigma^2$  are known with absolute certainty. This assumption may however not be valid in practice. The concept of the *expected power* (or *assurance*) aims at defining the power without conditioning on those parameters.

## 2 Expected power

For some parameter of interest  $\theta$ , the expected power is the (weighted) average power over all possible values of  $\theta$ . The weights are chosen according to the likelihood of an outcome to occur. More precisely, the expected power is defined as  $\mathbb{E}(\pi(\theta))$ , where the expectation is taken with respect to the probability distribution of  $\theta$ . It can therefore be seen as unconditional probability of success. In other words, the expected power does not assume that the parameter  $\theta$  is known but is estimated from a prior study and hence is associated with some uncertainty. It therefore provides a measure to deal with uncertainty regarding  $\theta$ . Depending on the setting we can consider  $\theta$  being  $\sigma^2$ ,  $\theta_0$  or  $(\theta_0, \sigma^2)$  and therefore deal with uncertainty with respect to either one of these choices.

How should the distribution for  $\theta$  be chosen? We define a prior distribution with respect to some pilot trial from which information on the treatment effect  $\theta_0$  and/or variability  $\sigma^2$  may be obtained. After observing the parameter of interest, the distribution will be updated to give a posterior distribution which is then used in the definition of the expected power (it is considered a prior distribution with respect to the trial to be planned).

### 3 Application to bioequivalence trials

#### 3.1 Uncertainty with respect to $\sigma^2$

We first deal with the case where uncertainty with respect to  $\sigma^2$  only should be accounted for. Consider the function  $\pi_{\theta_0} : \mathbb{R}_{>0} \rightarrow [0, 1]$ ,  $v \mapsto \pi(\theta_0, v)$ , where  $\theta_0 \in \mathbb{R}$  is some fixed value. We need to derive  $\mathbb{E}(\pi_{\theta_0}(\sigma^2))$ , i.e. the expected value with respect to  $\sigma^2$ . As prior distribution of  $\sigma^2$  we choose Jeffreys' prior as in [1] and [2, Example 6.26]. Thus, given the observed information  $\hat{\sigma}^2$  from the historical trial, the posterior distribution of  $\sigma^2$  is given by the inverse gamma distribution with shape and scale parameters  $\frac{\hat{v}_m}{2}$  and  $\frac{\hat{v}_m}{2} \cdot \hat{\sigma}^2$ , respectively, where  $\hat{\sigma}^2$  and  $\hat{v}_m$  denote the observed residual variance and degrees of freedom from the historical trial, respectively. Note that for this case Julious and Owen [3] provide an approximate formula for the expected power.

#### 3.2 Uncertainty with respect to $\theta_0$

Now consider the case where uncertainty with respect to only  $\theta_0$  should be dealt with. We consider the function  $\pi_{\sigma^2} : \mathbb{R} \rightarrow [0, 1]$ ,  $t \mapsto \pi(t, \sigma^2)$ , where  $\sigma^2 \in \mathbb{R}_{>0}$  is some fixed value. In order to derive  $\mathbb{E}(\pi_{\sigma^2}(\theta_0))$  we use Jeffreys' prior for  $\theta_0$  (with  $\sigma^2$  known) which leads to the posterior distribution  $N(\hat{\theta}_0, \frac{\sigma^2}{\lambda})$ , where  $\lambda = \left(\frac{\sigma}{\text{s\hat{e}m}_m}\right)^2$  and  $\text{s\hat{e}m}_m$  denotes the observed standard error of the difference of means from the historical trial, see [2, Example 6.26]. Note that in case of no missing data (and balanced sequences/groups) we have  $\frac{\sigma^2}{\lambda} = \frac{\text{b}k \cdot \sigma^2}{m}$ , where  $m$  is the total sample size of the historical trial.

#### 3.3 Uncertainty with respect to $\sigma^2$ and $\theta_0$

Finally, if uncertainty with respect to both parameters should be accounted for, consider the function  $\pi_{..} : \mathbb{R} \times \mathbb{R}_{>0} \rightarrow [0, 1]$ ,  $(t, v) \mapsto \pi(t, v)$ . For the expected power  $\mathbb{E}(\pi_{..}(\theta_0, \sigma^2))$  we use the reference prior  $d(\theta) \propto \sigma^{-2}$  for  $\theta = (\theta_0, \sigma^2)$  which leads to the normal-inverse-gamma distribution with parameters  $\mu = \hat{\theta}_0$ ,  $\lambda = \left(\frac{\hat{\sigma}}{\text{s\hat{e}m}_m}\right)^2$ ,  $\alpha = \frac{\hat{v}_m}{2}$ ,  $\beta = \frac{\hat{v}_m}{2} \cdot \hat{\sigma}^2$  as posterior distribution, [2, Example 6.26].

## Notes

- The distribution used in the first case (uncertainty with respect to  $\sigma^2$ ) coincides with the conditional distribution  $\sigma^2 \mid \theta_0 = \hat{\theta}_0$  from the joint posterior distribution (normal-inverse-gamma) from the last case (uncertainty with respect to both  $\sigma^2$  and  $\theta_0$ ).
- Similarly, in the second case the relevant distribution is the conditional distribution  $\theta_0 \mid \sigma^2 = \hat{\sigma}^2$ .
- While it is often the case that the expected power value is smaller than the classical conditional power value (for fixed sample size), this is in general not true.
- Moreover, the expected power may be bounded above by a value less than 1, see e.g. [5].

## 4 Implementation details

### 4.1 Uncertainty with respect to $\sigma^2$

We need to evaluate the integral

$$\mathbb{E}(\pi_{\theta_0}(\sigma^2)) = \int_0^\infty \pi_{\theta_0}(v) f(v) dv = \int_0^\infty \pi(\theta_0, v) f(v) dv,$$

where  $\pi$  is the classical conditional power function as a function in  $v$ ,  $\theta_0$  is some fixed real number and  $f$  is the density of the inverse gamma distribution with parameters as described in section 3.1. The practical implementation within `exppower.TOST` and `exppower.noninf` is performed via change of variables using the transformation  $v = \frac{u}{1-u}$  so that

$$\mathbb{E}(\pi_{\theta_0}(\sigma^2)) = \int_0^1 \pi\left(\theta_0, \frac{u}{1-u}\right) f\left(\frac{u}{1-u}\right) \cdot \frac{1}{(1-u)^2} du.$$

The expected power is then calculated according to the right hand side using `stats::integrate` with relative error tolerance of  $10^{-5}$ .

## 4.2 Uncertainty with respect to $\theta_0$

We need to evaluate the integral

$$\mathbb{E}(\pi_{\cdot\sigma^2}(\theta_0)) = \int_{-\infty}^{\infty} \pi_{\cdot\sigma^2}(t)f(t) \, dt = \int_{-\infty}^{\infty} \pi(t, \sigma^2)f(t) \, dt,$$

where  $\pi$  is the classical conditional power function as a function in  $t$ ,  $\sigma^2$  is some fixed positive number and  $f$  is the density of the normal distribution with parameters as described in section 3.2. The practical implementation within `exppower.TOST` and `exppower.noninf` is performed via change of variables using the transformation  $t = \frac{u}{1-u^2}$  so that

$$\mathbb{E}(\pi_{\cdot\sigma^2}(\theta_0)) = \int_{-1}^1 \pi\left(\frac{u}{1-u^2}, \sigma^2\right) f\left(\frac{u}{1-u^2}\right) \cdot \frac{1+u^2}{(1-u^2)^2} \, dt.$$

The expected power is then calculated according to the right hand side using `stats::integrate` with relative error tolerance of  $10^{-5}$ .

## 4.3 Uncertainty with respect to $\sigma^2$ and $\theta_0$

We need to evaluate the integral

$$\begin{aligned} \mathbb{E}(\pi_{\cdot\cdot}(\theta_0, \sigma^2)) &= \int_{(-\infty, \infty) \times (0, \infty)} \pi_{\cdot\cdot}(t, v)f(t, v) \, d(t, v) \\ &= \int_{-\infty}^{\infty} \int_0^{\infty} \pi_{\cdot\cdot}(t, v)f(t, v) \, dv \, dt \\ &= \int_{-\infty}^{\infty} \int_0^{\infty} \pi(t, v)f(t, v) \, dv \, dt, \end{aligned}$$

where  $\pi$  is the classical conditional power as a function in  $(t, v)$  and  $f$  is the density of the normal-inverse-gamma distribution with parameters as described in section 3.3. The practical implementation within `exppower.TOST` and `exppower.noninf` is performed via repeated change of variables using the transformation  $t = \frac{u}{1-u^2}$  and  $v = \frac{w}{1-w}$  so that

$$\mathbb{E}(\pi_{\cdot\cdot}(\theta_0, \sigma^2)) = \int_{-1}^1 \int_0^1 \pi\left(\frac{u}{1-u^2}, \frac{w}{1-w}\right) f\left(\frac{u}{1-u^2}, \frac{w}{1-w}\right) \cdot \left| \frac{1}{(1-w)^2} \cdot \frac{1+u^2}{(1-u^2)^2} \right| \, dw \, du.$$

The expected power is then calculated according to the right hand side using `cubature::hcubature` with maximum tolerance of  $10^{-4}$ .

## References

- [1] A. Bertsche, G. Nehmiz, J. Beyersmann, and A.P. Grieve. The predictive distribution of the residual variability in the linear-fixed effects model for clinical cross-over trials. *Biometrical Journal*, 58(4):797–809, 2016. doi: 10.1002/bimj.201500245.
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