The replication of equivalence studies

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Abstract  Replication studies are increasingly conducted to assess the credibility of scientific findings. Most of these replication attempts target studies with a superiority design, but there is a lack of methodology regarding the analysis of replication studies with alternative types of designs, such as equivalence. In order to fill this gap, we propose two approaches, the two-trials rule and the sceptical TOST procedure, adapted from methods used in superiority settings. Both methods have the same overall Type-I error rate, but the sceptical TOST procedure allows replication success even for non-significant original or replication studies. This leads to a larger project power and other differences in relevant operating characteristics. Both methods can be used for sample size calculation of the replication study, based on the results from the original one. The two methods are applied to data from the Reproducibility Project: Cancer Biology.

Keywords: Design of replication studies; Equivalence; Replicability; Sceptical p-value; Two-trials rule; Type-I error control

1 Introduction

Replicability of scientific findings is the gold standard to assess their credibility. Recent years have witnessed an increased interest in large-scale replication projects, aiming to reproduce the results found in an
original study in one or several replication studies. Various empirical domains of science are involved in these replication efforts: psychology (Open Science Collaboration 2015), social sciences (Camerer et al. 2016), economics (Camerer et al. 2018) and more recently cancer biology (Errington et al. 2021), among others.

In the majority of these endeavors, there is evidence against a point null hypothesis in the original study, i.e. the original effect estimate is significant or borderline significant. A replication study is then conducted to confirm the initial result and a significant replication effect estimate in the same direction is generally interpreted as a successful replication. Requiring two statistically significant studies is analogous to the two-trials rule in drug development (FDA 1998). But the two-trials rule is not the only criterion used in the assessment of replication success; many replication projects also consider other measures such as compatibility of the effect estimates from both studies and meta-analysis of these estimates. Furthermore, there is a growing body of literature on the design and analysis of such replication studies, and new methodology is emerging (e.g. in Anderson and Maxwell 2017; Bonett 2020; Held 2020; Hedges and Schauer 2021; Micheloud and Held 2022; Held et al. 2022; Micheloud et al. 2023).

However, it might also happen that original studies with a ‘null result’, i.e. with a $p$-value considerably larger than the significance level, are selected for replication. This was for example the case for 15 out of 112 effects in the Reproducibility Project Cancer Biology (RPCB, Errington et al. 2021) and for 3 out of 100 studies in the Reproducibility Project Psychology (RPP, Open Science Collaboration 2015). One criterion for replication success of such effects was a non-significant replication effect estimate. However, interpreting a non-significant effect as null can be misleading, as the apparent null effect could in reality be caused by a low sample size, which, if increased, would render the same effect statistically significant. This issue has also been pointed out by Pawel et al. (2024). In fact, if the aim of the original (and subsequently the replication) study is to show that an effect is null, then another type of design needs to be used in both studies: an equivalence design. Equivalence studies are conducted to show the opposite of superiority studies, namely that an effect $\theta$ is sufficiently close to 0 that it can be considered negligible. Because it is impossible to accept a point hypothesis, an interval of equivalence $[-\delta; \delta]$ needs to be specified (Serlin and Lapsley 1985). In clinical trials regulations, the International Conference on Harmonisation (ICH) E9 (ICH E9 Expert Working Group 1999, p. 18) states that the margin $\delta$ is ‘the largest difference that can be judged as being clinically acceptable and should be smaller than differences observed in superiority trials of the active comparator’. The composite hypotheses $H_0 : \theta \not\in [-\delta, \delta]$ and $H_1 : \theta \in [-\delta, \delta]$ can be decomposed into two one-sided hypothesis pairs, namely

$$H_{0}^{+} : \theta \geq \delta \text{ vs. } H_{1}^{+} : \theta < \delta$$ (1)
and

\[ H_0^- : \theta \leq -\delta \text{ vs. } H_1^- : \theta > -\delta. \]  

(2)

This decomposition is the basis of a widely used method in the assessment of equivalence known as the ‘two one-sided tests (TOST)’ procedure (Schuirmann, 1987). Equivalence of the unknown effect \( \theta \) is declared if and only if both null hypotheses in (1) and (2) are rejected in favor of the alternative at the one-sided nominal level of significance \( \alpha \). An alternative, equivalent approach is to calculate a \((1 - 2\alpha)\%\) confidence interval for \( \theta \) and conclude equivalence if it falls entirely within the interval \([-\delta; \delta]\). The Type-I error rate of the TOST procedure, \textit{i.e.} the probability to incorrectly declare equivalence, depends on the value of the true effect \(|\theta| \geq \delta\), and is at most \( \alpha \) (Matthews, 2006, Section 11.5.2).

Equivalence designs have been used for many years now, especially in clinical trials and pharmacokinetics, and the methodology has been extensively discussed. Similarly, replication studies are very popular nowadays, and numerous methods for their design and analysis in the superiority setting have been proposed. However, there has been little interest so far in combining the two topics: the original study has an equivalence design and the replication aims to confirm this equivalence. The primary aim of this paper is hence to fill this gap and to present methodology to analyze and design equivalence replication studies. In particular, we investigate in detail the theoretical properties and the error rates of applying the TOST procedure twice (simply called the two-trials rule here) as proposed in Pawel et al. (2024). Furthermore, we develop the ‘sceptical TOST procedure’, which stems from the sceptical \( p \)-value (Held, 2020), a reverse-Bayes method to assess replicability in superiority studies. In Micheloud et al. (2023), a recalibration gives rise to the \textit{controlled sceptical} \( p \)-value, ensuring the same Type-I error rate as the two-trials rule when the true effect is null in both studies. The controlled sceptical \( p \)-value has a number of advantages over the two-trials rule in the superiority setting, which are summarized in Section 2.2.

The paper is structured as follows: The two-trials rule applied to equivalence studies and the sceptical TOST procedure are presented and their properties are described in Section 2. The two methods are then further compared in Section 3 with a focus on power and Type-I error rate. Sample size calculations for an equivalence replication study using the information provided by the original result are described in Section 4. Finally, some discussion is provided in Section 5. Two study pairs from Errington et al. (2021) are presented in Section 1.2 and will be used as running examples.

### 1.1 Statistical framework

In our framework the original and replication effect estimates \( \hat{\theta}_o \) and \( \hat{\theta}_r \) are assumed to be normally distributed around the unknown effects \( \theta_o \) and \( \theta_r \), respectively, with standard error \( \sigma_o \) and \( \sigma_r \). The squared
standard errors can generally be expressed as $\sigma_o^2 = \kappa^2/n_o$ and $\sigma_r^2 = \kappa^2/n_r$ where $\kappa^2$ is some unit variance and $n_o$ and $n_r$ the original and replication sample sizes, respectively. The variance ratio $c = \sigma_o^2/\sigma_r^2$ then reduces to the relative sample size $c = n_r/n_o$. This also holds in the balanced two-sample case where $\sigma_i^2 = 2\kappa^2/n_i$, $i \in \{o, r\}$, with $n_i$ the sample size per group. The equivalence interval $[-\delta; \delta]$ is assumed to be symmetric around 0 and identical for the original and the replication study. Furthermore, the one-sided significance level $\alpha$ is set to 5%, and $z_\alpha = \Phi^{-1}(1-\alpha)$ is the $(1-\alpha)$-quantile of the standard normal distribution function, with $\Phi(\cdot)$ its cumulative distribution function. Without loss of generality, the original effect estimate $\hat{\theta}_o$ is assumed to be positive and smaller than the margin $\delta$.

A focus of this paper is Type-I error (T1E) control, so definitions of the relevant null hypotheses are required. The study-specific null hypotheses are denoted by $H_{i0}$, $i \in \{o, r\}$, and depend on the design type: $H_{o0}: \theta_i = 0$ for superiority and $H_{r0}: \theta_i \notin [-\delta; \delta]$ for equivalence. We follow Heller et al. (2014) and Micheloud et al. (2023) and differentiate between the intersection null hypothesis

$$H_{o0} \cap H_{r0}$$

and the union null hypothesis

$$H_{o0} \cup H_{r0}.$$ 

The probability of a false claim of replication success associated with these two hypothesis types are the overall and the partial T1E rate, respectively. The risk of a false claim of replication success if the replication study sample size is properly selected based on the original study result is referred to as the conditional T1E rate.

1.2 Examples

In order to illustrate our methodology, we will use two study pairs from Errington et al. (2021) (dataset available at https://osf.io/39s7j). In this project, a nested structure was employed, where each paper selected for replication contained several experiments. These experiments, in turn, encompassed more than one effect of interest, and finally, certain effects were replicated in multiple internal replications. Original effects with a non-significant $p$-value were termed ‘null’ by Errington et al. (2021), and replication success was achieved with a non-significant replication study. As discussed before, this approach is problematic as non-sigificance in both studies does not guarantee that there is evidence for no effect (Pawel et al., 2024). In the original study from Goetz et al. (2011) (Paper #20, Experiment #1, Effect #1 in Errington et al., 2021), there was no evidence for a treatment effect (two-sided $p = 0.34$). The replication team also failed to find
a significant effect (Internal replication #1, $p = 0.83$), hence replication success was declared. In contrast, the non-significant result in the original study by [Lin et al., 2012] (Paper #48, Experiment #2, Effect #4) was not successfully replicated, as a significant effect estimate was detected in the replication study (Internal replication #2, two-sided $p < 0.0001$).

The dataset gives the results as correlation coefficients $r$. We transform them with Fisher $z$-transformation $z = \text{arctanh}(r)$ to achieve a normal distribution. The standard error of $z$ is a function of the effective sample size $n - 3$ only: $\text{se}(z) = \frac{1}{\sqrt{n - 3}}$. Figure 1 shows the original and replication effect estimates (on Fisher’s $z$-scale) with their 90%-CI, so $\alpha = 5\%$. The standard errors are $\sigma_\text{o} = 0.18$ and $\sigma_\text{r} = 0.13$ and so $c = \sigma_\text{o}^2 / \sigma_\text{r}^2 = 1.9$ in the first study pair, and $\sigma_\text{o} = 0.06$ and $\sigma_\text{r} = 0.04$ and so $c = \sigma_\text{o}^2 / \sigma_\text{r}^2 = 2.1$ in the second study pair. Note that the variance ratio $c$ is equal to the ratio (replication to original) of the effective sample sizes. These study pairs will serve as running examples to illustrate our methodology and to highlight why non-significant effects should not be misinterpreted as bearing evidence for no effect.

In equivalence designs, the margin should ideally be chosen by experts in the field before the first study is conducted, but post-hoc margin specification is also possible [Campbell and Gustafson, 2021]. As no margin was pre-specified in [Goetz et al., 2011] and [Lin et al., 2012], we have to select the margins. Wellek (2010, Table 1.1) defines a strict margin to be $d_\text{S} = 0.36$ and a liberal margin $d_\text{L} = 0.74$ on Cohen’s $d$ scale.

In Figure 1: Original study by Goetz et al. (2011) and its replication by Sheen et al. (2019) and original study by Lin et al. (2012) and its replication (Blum et al., 2015). Shown are the effect estimates on Fisher’s $z$-scale with 90% original and replication confidence intervals: $[-0.13; 0.47]$ and $[-0.19; 0.24]$, respectively, in the first study pair, and $[-0.01; 0.19]$, respectively $[-0.28; -0.14]$ in the second study pair. The $p$-values in black are two-sided $p$-values from the superiority tests, while the $p$-values in color are one-sided $p$-values from the TOST procedure as explained in Section 2.1. The strict $d_\text{S} = 0.18$ and the liberal $d_\text{L} = 0.36$ margins are indicated with colors. The original and replication effect estimates in the second study pair have been re-oriented to make $\hat{\theta}$ positive.
This translates to $\delta_s = 0.18$ and $\delta_l = 0.36$ on Fisher’s $z$-scale, respectively (Ruscio 2008). For illustration purposes, we chose to use the liberal margin in the first example, and the strict margin in the second. These margins might seem large, however, a systematic review of the margins in non-inferiority and equivalence clinical trials revealed that 50% of the trials had a margin larger than $d = 0.5$, and 5% even had a margin larger than $d = 1$ (Lange and Freitag 2005).

2 Methods

In this section, two approaches are presented: the two-trials rule for equivalence studies (Section 2.1) and the sceptical TOST procedure (Section 2.2), summarized in Figure 3. Some properties of both methods are then described (Section 2.3) and an application is given in Section 2.4.

2.1 Two-trials rule

The two-trials rule applied to an equivalence design amounts to applying the TOST procedure twice – once for the original and once for the replication study (Pawel et al. 2024). This results in four one-sided tests with corresponding $z$-values defined as

$$
z_{o+} = (\hat{\theta}_o - \delta)/\sigma_o, \quad z_{r+} = (\hat{\theta}_r - \delta)/\sigma_r \quad \text{for } H_{o+}^+ \text{ in (1), and}
$$

$$
z_{o-} = (\hat{\theta}_o + \delta)/\sigma_o, \quad z_{r-} = (\hat{\theta}_r + \delta)/\sigma_r \quad \text{for } H_{o-}^- \text{ in (2)}.
$$

The $z$-values $z_{i+}$ and $z_{i-}$, $i \in \{o, r\}$, are related to each other via

$$
z_{i-} = \left(\frac{f_i + 1}{f_i - 1}\right) z_{i+}, \quad (3)
$$

with

$$f_i = \hat{\theta}_i / \delta.$$

The $z$-values are then transformed to $p$-values using $p_{i+} = \Phi(z_{i+})$ and $p_{i-} = 1 - \Phi(z_{i-}), i \in \{o, r\}$. The two-trials rule is fulfilled if $p_{\text{max}} = \max\{p_{o+}, p_{r+}\} < \alpha$, with $p_{o+} = \max\{p_{o+}, p_{r+}\}$ and $p_{r+} = \max\{p_{o+}, p_{r+}\}$, see Figure 3. Note that with a positive original effect estimate $\hat{\theta}_o$, $p_{o-}$ is always smaller than $p_{o+}$, and so $p_{\text{max}} = p_{o+}$. 

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2.2 The sceptical TOST procedure

The sceptical TOST procedure is an adaptation of the sceptical $p$-value which has so far only been developed for superiority studies. The theory behind the sceptical $p$-value is first briefly summarized, and our adaptation to equivalence studies is then presented.

**Superiority studies** [Held (2020)] proposed the sceptical $p$-value, a new approach to declare replication success in superiority studies based on two steps: the analysis of credibility [Matthews, 2001a,b] and a prior-predictive check for conflict [Box, 1980]. In a nutshell, a significant original result at level $\alpha$ is combined with a sceptical prior centered around zero, and with variance chosen such that the significant result is no longer convincing (lower limit of the $(1 - \alpha) \times 100\%$ posterior credible interval is exactly equal to 0). If there is sufficient conflict between the sceptical prior and the replication result, the sceptical prior is deemed unrealistic and replication success is declared. The quantitative measure of replication success resulting from this procedure is the sceptical $p$-value, which only depends on the study-specific $p$-values $p_o$ and $p_r$, and the relative sample size $c$. Replication success is achieved if the sceptical $p$-value is smaller than the level $\alpha$.

The original formulation was recently recalibrated by [Micheloud et al. (2023)] to give rise to the controlled sceptical $p$-value $p_S$ which ensures that the overall T1E rate is exactly controlled at $\alpha^2$. The theory in [Micheloud et al. (2023)] has also shown that the corresponding partial T1E rate is bounded by $\gamma_c > \alpha$, see Figure 2. The controlled sceptical $p$-value (simply called the sceptical $p$-value from now on) hence does not impose a strict dichotomization at $\alpha$ for the original and replication $p$-values as the two-trials rule, and success is even possible for non-significant original or replication studies as long as the two $p$-values are smaller than $\gamma_c$. Attractive properties of the approach include an increased project power to detect existing effects over both studies in combination and the possibility to calculate the replication sample size even for non-significant original studies. Moreover, the conditional T1E rate is sufficiently bounded [Micheloud et al. (2023) Section 3.4].

**Equivalence studies** We now adapt the sceptical $p$-value to the replication of equivalence studies. As there are two sets of hypotheses (1) and (2), the procedure explained above for superiority studies needs to be carried out twice, with sceptical priors centered around $\delta$ and $-\delta$, respectively. The sceptical $p$-value $p_S^+$ measuring the conflict between the sceptical prior centered at $\delta$ and the replication data now depends on $p_o^+$, $p_r^+$ and $c$, see Figure 3. Similarly, the sceptical $p$-value $p_S^-$ measuring the conflict between the sceptical prior centered at $-\delta$ and the replication data depends on $p_o^-$, $p_r^-$ and $c$. Replication success is achieved if $p_S^{max} = \max\{p_S^+, p_S^\} < \alpha$. 

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Figure 2: Bound \( \gamma_c \) on the partial TIE rate for superiority studies as a function of the relative sample size \( c \) for \( \alpha = 0.05 \).

### 2.3 Necessary conditions for replication success

In superiority studies, the necessary replication success condition on the study-specific \( p \)-values is \( p^\text{max} < \alpha \) with the two-trials rule (which is also a sufficient condition) and \( p^\text{max} < \gamma_c \) (which is not sufficient) with the sceptical \( p \)-value. The derivation of necessary bounds is more involved for equivalence studies. We will use the same procedure for both methods.

First, the conditions \( p^\text{max} < \alpha \) and \( p^\text{max}_S < \alpha \), respectively, are rewritten as success intervals for \( z^+_r \), which depend on \( z^+_o, f_o \) and \( c \). We will then show that success is impossible if \( z^+_o \) is larger than a certain value. This particular value of \( z^+_o \) is transformed into a \( p \)-value \( p^+_o \) which defines the largest value of \( p^+_o \) for which replication success is possible. The same procedure is then applied to obtain the necessary condition on \( p^+_r \).

The details are provided in what follows.

**Two-trials rule** The condition \( p^\text{max}_r < \alpha \) can be rewritten as a success region for \( z^+_r \) conditional on the original study result:

\[
z_o - \frac{2z_o^+ \sqrt{c}}{f_o - 1} < z^+_r < -z_o,
\] (4)
Figure 3: Summary of the assessment of replication success for equivalence studies with the two-trials rule and the sceptical TOST procedure.

see Appendix A for details. However, if \( z_o^+ > z_\alpha (f_o - 1)/\sqrt{c} \), Equation 4 cannot be fulfilled as the lower bound for \( z_o^+ \) is larger than the upper one. Combining this with the condition \( z_o^- < -z_\alpha \), the necessary condition on \( z_o^+ \) for replication success is

\[
z_o^+ < z_\alpha \min\{(f_o - 1)/\sqrt{c}, -1\}.
\]  

The right-hand side of (5) is then transformed into an upper bound on the corresponding p-value \( p_o^+ \) for which the two-trials rule can be fulfilled. Note that this upper bound cannot be larger than \( \alpha \). Similarly, the condition \( p_o^+ < \alpha \) can be rewritten as a success region for \( z_o^+ \), and the largest value of \( p_r^+ \) for which the two-trials rule can be fulfilled based on \( f_r \) and \( c \) can be derived, see Appendix B for detail.
Sceptical TOST procedure  The replication success condition \( p^{\text{rep}}_{S} < \alpha \) can be expressed as a success region for \( z_{+} \) conditional on the original study result,

\[
z_{\gamma} \left[ 1 + c \left\{ \frac{1}{2} K_{o}^{+} - 1 \right\} \right] \leq z_{+} \leq -z_{\gamma} \left[ 1 + c \left\{ \frac{1}{2} K_{o}^{+} - 1 \right\} \right],
\]

with \( K_{o}^{+} = \left( z_{+} / z_{\gamma} \right)^{2} \), where \( z_{\gamma} = \Phi^{-1} (1 - \gamma c) \). Details are given in Appendix A. Success is thus impossible if \( (z_{+})_{\text{lower}} > (z_{+})_{\text{upper}} \), and root-finding algorithms can be used to calculate the smallest value of \( z_{+} \) where this happens. This corresponds to an upper bound on \( p^{+}_{o} \). Equation (6) can similarly be rewritten as a success region for \( z_{+} \), and the upper bound on \( p^{+}_{r} \) can be derived.

Comparison of the two methods  Figure 4 shows the upper bound on \( p^{+}_{o} \) (left) and \( p^{+}_{r} \) (right) with the two-trials rule and the sceptical TOST procedure as a function of \( f_{o} \) and \( f_{r} \), respectively. Necessary conditions on \( p^{-}_{o} \) and \( p^{-}_{r} \) can be obtained directly from the necessary conditions on \( p^{+}_{o} \) and \( p^{+}_{r} \) using Equation (3), and are not shown. With both methods, the upper bound on \( p_{i}^{+} \), \( i \in \{o, r\} \), increases as a function of \( f_{i} \). This makes sense, as the closer \( f_{i} \) is to one, the smaller \( p_{i}^{-} \) is (see Equation (3)) and so the more convincing the study is. The two-trials rule has the in-built condition \( p_{i} < \alpha \), explaining the plateau at 0.05. The sceptical TOST procedure, on the other hand, tends to \( \gamma c > \alpha \) for \( f_{i} \rightarrow 1 \), as in the superiority case. The influence of \( c \) differs in the two plots. The upper bound on \( p^{+}_{o} \) increases as a function of \( c \), while it depends on \( f_{r} \) for the upper bound on \( p^{+}_{r} \).

To summarize, the necessary condition on the study specific \( p \)-values \( p^{+}_{o} \) and \( p^{+}_{r} \) is usually more stringent with the two-trials rule than with the sceptical TOST procedure. Non-significant studies can lead to replication success with the latter method, but not with the former.

2.4 Application  The two methods are now applied to both examples presented in Figure 1. Table 1 shows \( p^{\text{max}} \) from the two-trials rule and \( p^{\text{max}}_{S} \) from the sceptical TOST procedure. In both examples, \( p^{\text{max}} \) and \( p^{\text{max}}_{S} \) are similar in magnitude. In the first study pair (Goetz et al., 2011), both methods lead to the opposite conclusion to that of the replication team: replication success cannot be declared at level \( \alpha = 0.05 \) as \( p^{\text{max}} = 0.14 \) and \( p^{\text{max}}_{S} = 0.10 \). However, at level \( 0.10 < \alpha < 0.14 \), the sceptical TOST procedure would flag replication success but not the two-trials rule, highlighting that significance of both studies is not required with the former approach. Replication success cannot be declared with either method in the second study pair (Lin et al., 2012), regardless of the level \( \alpha \) as the replication effect estimate \( \hat{\theta}_{r} \) is larger than the margin \( \delta \) (in absolute
Figure 4: Upper bound on $p_{o}^{+}$ (left) or $p_{r}^{+}$ (right) for replication success with the two-trials rule and the sceptical TOST procedure as a function of $f_{o}$ or $f_{r}$ for relative sample size $c \in \{0.5, 1, 10\}$ with $\alpha = 0.05$.

| Study       | $\hat{\theta}_{o}$ | $\hat{\theta}_{r}$ | $\delta$ | two-trials rule | sceptical TOST |
|-------------|----------------------|----------------------|-----------|-----------------|----------------|
|             | $p_{o}^{max}$ | $p_{r}^{max}$ | $p_{o}^{max}$ | $p_{r}^{max}$ | $p_{S}$ | $p_{S}^{+}$ | $p_{S}^{max}$ |
| Goetz et al | 0.17    | 0.03    | 0.36    | 0.14   | 0.005 | **0.14** | 0.003 | 0.10 | **0.10** |
| Lin et al   | 0.09    | -0.21   | 0.18    | 0.062  | 0.78  | **0.78** | 0.84  | 0.016 | **0.84** |

Table 1: Original and replication effect estimates, margin, two-trials rule and sceptical TOST $p$-values of the running examples.

### 3 Power and Type-I error rate

Suppose now that neither of the two studies has been conducted yet. Of great interest are the operating characteristics of the two methods. In particular, our focus lies in the probability to declare replication success under the alternative hypothesis that both effects are exactly $0$ (project power), the intersection null that both effects are at the margin $\delta$ (overall TIE rate), and under the union null that at least one effect is at the margin $\delta$ (partial TIE rate). The TIE rate varies with the value of $\theta \geq \delta$ and reaches a maximum for $\theta = \delta$.
so the overall and partial T1E rates represent upper bounds.

### 3.1 Project power

Let’s denote the power of the original study to detect perfect equivalence ($\theta = 0$) by $1 - \beta$. The power of a replication study of size $n_r = cn_o$ to reach a significant TOST procedure is then $2\Phi (c\mu - z_\alpha) - 1$, with $\mu = z_{\beta/2} + z_\alpha$ (Matthews, 2006, Section 11.5.2), where $z_{\beta/2} = \Phi^{-1} (1 - \beta/2)$. The project power of the two-trials rule is the product of the two,

$$(1 - \beta)\Phi (c\mu - z_\alpha - 1),$$

as original and replication studies are independent. The project power of the TOST procedure is the probability of (6) under the alternative hypothesis that the effect is exactly 0 in both studies. The lower bound $(z^+_\text{lower})$ in (6) depends on $f_o$ which can be rewritten as $f_o = z^+_o / \mu + 1$. Using the distributions $z^+_o \sim \mathcal{N}(-\mu, 1)$ and $z^+_r \sim \mathcal{N}(\mu \sqrt{c}, 1)$ under the alternative hypothesis of perfect equivalence, the project power is

$$\int_a^b \left\{\Phi \left\{ (z^+_r)_{\text{lower}} + \mu \sqrt{c} \right\} - \Phi \left\{ (z^+_r)_{\text{upper}} + \mu \sqrt{c} \right\} \right\} \phi(z^+_o + \mu) dz_o^+,\$$

where

$$a = z_\gamma - \mu \text{ and } b = -z_\gamma + \mu.$$  

Figure 5 (a) shows the project power as a function of the relative sample size $c$ for an original power $1 - \beta$ of 80%. The project power of the sceptical TOST procedure is always larger than of the two-trials rule, and is even larger than the original power for large values of the relative sample size $c$.

### 3.2 Overall T1E rate

The T1E rate of the original study depends on $1 - \beta$, the original power to detect perfect equivalence ($\theta_o = 0$). Namely, it is

$$\alpha - \Phi(-2z_{\beta/2} - z_\alpha),$$

so it tends to $\alpha$ as $1 - \beta$ increases. Similarly, the replication T1E rate is

$$\alpha - \Phi(-2\sqrt{c}\mu + z_\alpha)$$
and depends both on the original power and the replication sample size $n_r = cn_o$. Because of independence of the two studies, the overall T1E rate of the two-trials rule is the product of (8) and (9).

Under the intersection null hypothesis that both effects are at the margin $\delta$, $z_o^+ \sim N(0, 1)$ and $z_r^+ \sim N(0, 1)$. Using (6), the overall T1E rate of the sceptical TOST procedure is hence

$$
\int_a^b \left[ \Phi \left\{ \left( z_r^+ \right)_{\text{upper}} \right\} - \Phi \left\{ \left( z_r^+ \right)_{\text{lower}} \right\} \right] \phi(z_o^+)dz_o^+ ,
$$

with $a$ and $b$ defined in (7). The overall T1E rate of both strategies is almost the same (see Figure 5 (b)): It starts at 0 for small relative sample sizes $c$ and increases up to $\alpha^2 = 0.05^2 = 0.0025$. This is in line with how the controlled sceptical $p$-value for superiority studies was constructed to match the overall T1E rate of the two-trials rule. It is not constant at $\alpha^2$ as in the superiority setting as the replication power to detect perfect equivalence also matters here and is low for small relative sample sizes $c$.

### 3.3 Partial T1E rate

The partial T1E rate is the probability of a false claim of replication success with respect to the union null hypothesis. We assume here that there is perfect equivalence in the first study ($\theta_o = 0$) and no equivalence in the second study ($\theta_r = \delta$). The partial T1E rate of the two-trials rule is the product of the original power $1 - \beta$ and the replication T1E rate expressed in (9), because of independence of the two studies.

The distributions of $z_o^+$ and $z_r^+$ are $z_o^+ \sim N(\mu, 1)$ and $z_r^+ \sim N(0, 1)$. Using (6), the partial T1E rate of the sceptical TOST procedure is hence

$$
\int_a^b \left[ \Phi \left\{ \left( z_r^+ \right)_{\text{upper}} \right\} - \Phi \left\{ \left( z_r^+ \right)_{\text{lower}} \right\} \right] \phi(z_o^+ + \mu)dz_o^+ .
$$

The partial T1E rate of both methods is shown in Figure 5(c). For the same reason as explained in the previous section, it is 0 for small relative sample sizes $c$. Moreover, the partial T1E rate of the two-trials is constant at $0.05 \times 0.8 = 4\%$ if the relative sample size $c$ is large enough. In contrast, the T1E of the sceptical TOST procedure increases with $c$, and does not reach a plateau but is always smaller than $\gamma_c$. In a sense, the increase in partial T1E rate is the price to pay for the increase in project power of the sceptical TOST procedure. However, in practice the relative sample size $c$ is not fixed but chosen based on the original study. As a result, there is another T1E rate that is more suited than the partial T1E rate: the conditional T1E rate described in Section 4.4.
Figure 5: Project power, overall T1E rate, and partial T1E rate of the two-trials rule and the sceptical TOST procedure. The original study has a power of 80% to detect perfect equivalence ($\theta_o = 0$).

4 Design of replication studies

The previous section assumes that none of the equivalence studies have been conducted yet. Here we assume that the results of the original study are available, and use them to calculate the sample size of the replication. As the design of a replication study should always match the planned analysis method (Anderson and Kelley, 2022), we provide sample size calculations for the two-trials rule and the sceptical TOST procedure.

4.1 Sample size calculation

In superiority studies, the replication sample size is usually chosen such that the conditional power to detect the original effect estimate $\hat{\theta}_o$ at level $\alpha$ reaches a certain value (typically between 80 and 95%). This is the approach which has been taken in the Reproducibility Project: Cancer Biology (Errington et al., 2021) for the replication of significant original studies. However, this approach does not work for the original studies with a null result as $\hat{\theta}_o$ is very close to 0. For these studies, the replication teams selected the sample size based on a sensitivity analysis, see the corresponding registered reports for more information (Fiering et al., 2015; Blum et al., 2015). This demonstrates the need for an appropriate sample size method targeted towards equivalence studies, as explained in this section. We assume here that the true effect $\theta_o = \theta_r = \theta$ is the same in both studies.
**Two-trials rule** The replication power of the TOST procedure can be calculated using the confidence interval perspective. Namely, it is the probability that the estimate \( \hat{\theta}_r \) lies within \( [-\delta + z_\alpha \sigma_r; \delta - z_\alpha \sigma_r] \). Now \( \hat{\theta}_r \) is \( N(\theta, \sigma_r) \) distributed, so the power of the replication study at significance level \( \alpha \) is

\[
\Phi \left( \frac{\delta - \theta}{\sigma_r} - z_\alpha \right) - \Phi \left( \frac{-\delta - \theta}{\sigma_r} + z_\alpha \right).
\]

This corresponds to the standard power formula for equivalence studies (Flight and Julious, 2015, Equation (5)). If the true effect size \( \theta \) is assumed to be exactly 0, the power simplifies to \( 2\Phi(\delta/\sigma_r - z_\alpha) - 1 \). However, the original effect estimate \( \hat{\theta}_o \) is a much more suited replacement for \( \theta \). In our approach, we want to express the power on the relative scale and this gives the conditional power:

\[
CP_\text{2TR} = \Phi \left( \frac{-z_\alpha^+ \sqrt{c} - z_\alpha}{A} \right) - \Phi \left( \frac{-z_\alpha^- \sqrt{c} + z_\alpha}{B} \right). \tag{10}
\]

This approach assumes that the effect \( \hat{\theta}_o \) detected in the original study is the unknown, true effect \( \theta \) and ignores its inherent uncertainty. Uncertainty of the original effect estimate \( \hat{\theta}_o \) is acknowledged in the power calculation if the predictive distribution

\[
\hat{\theta}_r \sim N \left( \hat{\theta}_o, \sigma_o^2 + \sigma_r^2 \right) \tag{11}
\]

is used. This leads to the predictive power,

\[
PP_\text{2TR} = \Phi \left( \frac{A}{\sqrt{c + 1}} \right) - \Phi \left( \frac{B}{\sqrt{c + 1}} \right). \tag{12}
\]

Predictive power thus is not conditional on a single value for \( \theta \), but instead uses a distribution of potential \( \theta \) values provided by the original study. The concept of predictive power has first been proposed by Spiegelhalter and Freedman (1986) to provide a more direct predictive interpretation than conditional power. In the context of replication studies it has been discussed in Micheloud and Held (2022) and Held et al. (2022) for superiority designs. Its use has also been investigated for (bio)equivalence studies (O’Hagan et al., 2005; Ring et al., 2019, Section 2.1.4).

**Sceptical TOST procedure** Equation (3) can also be used to derive the conditional power with the sceptical TOST procedure. The only difference as compared to the project power is that \( z_o^+ \) and \( f_o \) are now fixed.
as the results of the original study are known. The conditional power is then the probability of (6), namely
\[
CP_{R} = \Phi\left(-z_o^+ \sqrt{c} - z_\gamma \sqrt{1 + c/(K_o^+ - 1)}\right) - \Phi\left(-z_o^- \sqrt{c} + z_\gamma \sqrt{1 + c/(K_o^- - 1)}\right).
\]
(13)

The predictive power turns out to be
\[
PP_{R} = \Phi\left(\frac{C}{\sqrt{c+1}}\right) - \Phi\left(\frac{D}{\sqrt{c+1}}\right).
\]
(14)

The four power formulas (10), (12), (13), (14) all contain two terms. Due to these two components, the required relative sample size \(c\) to reach a fixed power in the equivalence setting cannot be derived by simply inverting the power formulas as in the superiority framework. Instead, application of root-finding algorithms is necessary.

### 4.2 Properties

Figure 6 compares the required relative sample size \(c\) to reach a conditional and predictive power of 80\% with the two-trials rule and the sceptical TOST procedure. Two cases are explored: \(f_o = 0.1\), meaning the original effect estimate \(\hat{\theta}_o\) was close to 0, and \(f_o = 0.9\), meaning that \(\hat{\theta}_o\) was close to the margin \(\delta\). With both methods, the required relative sample \(c\) size is slightly smaller for larger \(f_o\) as for a fixed \(p_o^+\), \(p_o^-\) decreases for increasing \(f_o\). Furthermore, the required sample size is smaller with the sceptical TOST procedure as compared to the two-trials rule for more convincing original studies, and larger for original studies with a \(p\)-value \(p_o^+\) close to \(\alpha = 0.05\). But the main difference between the two approaches is that, while \(p_o^{max} < 0.05\) is required in two-trials rule, there is no such dichotomization in the sceptical TOST procedure, where sample size calculation is also possible based on non-significant original studies. With conditional power, it is possible as long as \(\hat{\theta}_o < \delta\), i.e. \(p_o^+ < 0.5\), while it depends on the values \(f_o\) and the target power with predictive power. For a predictive power of 80\%, replication sample size calculation is possible if \(p_o^+ < 0.13\) for \(f_o = 0.1\) and if \(p_o^+ < 0.21\) for \(f_o = 0.9\). As in superiority studies, predictive power is typically smaller than conditional power with both methods, hence a larger replication sample size is required if the calculation is based on the former (Micheloud and Held, 2022).

Note that the upper bound on \(p_o^+\) and \(p_o^-\) with the sceptical TOST procedure is at most \(\gamma_c\) (see Figure 4), which increases with \(c\). This means that a large relative sample size \(c\) will make replication success in theory possible even if one of the \(p\)-values is very large. This might seem controversial, however, we will show in Section 4.4 that the T1E rate of the replication study, conditional on the original study results, gets smaller for larger \(p_o^+\), and so for larger relative sample sizes \(c\). This point will also be further discussed in Section 5.
4.3 Sample size recalculation

Using the appropriate equivalence methods developed above, the required relative sample size \(c\) has been recalculated based on the original studies by Goetz et al. (2011) and Lin et al. (2012). For a conditional power of 80% and \(\alpha = 0.05\), a relative sample size of \(c = 21.1\) is required with the sceptical TOST procedure in the former study, and \(c = 4.2\) in the latter. In both cases, the required relative sample size is larger than the one which was actually used in the two replication studies (\(c = 1.9\), and \(c = 2.1\), respectively). No replication sample size can be calculated with the two-trials rule as \(p_o^+ + p_o^- > 5\%\) in both original studies.

4.4 Conditional T1E rate

It is also possible to calculate the conditional Type-I error rate, i.e. the T1E rate of the replication study, conditional on the original study result (Micheloud et al., 2023). To do so, the relative sample size \(c\) to reach a certain power based on a particular original result \((p_o^+, f_o)\) is calculated using the methodology presented in Section 4.1. The probability of \((6)\) with the relative sample size \(c\) and the null distribution \(z^+ \sim N(\mu, \sqrt{c}, 1)\) then gives the conditional T1E rate.

Figure 6 (bottom) shows the conditional T1E rate of both methods as a function of \(p_o^+\). The relative sample size \(c\) shown on the top axis is calculated using the sceptical TOST method to reach a conditional power of 80% and is very similar for \(f_o = 0.1\) (first row) and \(f_o = 0.9\) (second row). Regardless of \(f_o\), the conditional T1E rate of the two-trials rule is fixed at \(\alpha = 5\%\), provided that \(p_o^+ < 5\%\). In contrast, the conditional T1E rate of the sceptical TOST procedure is smaller than 5% if \(p_o^+ < 0.019\), and larger otherwise. However, it does not exceed 7.5% (for \(f_o = 0.1\)) and 7.3% (for \(f_o = 0.9\)) for a conditional power of 80%. For a conditional power of 90% and 95%, these maximum values are 7.8% (\(f_o = 0.1\)) and 7.7% (\(f_o = 0.9\)), and 8% (both \(f_o = 0.1\) and \(f_o = 0.9\)), respectively. It is thus always smaller than 2\(\alpha\) as in the superiority setting (Micheloud et al., 2023, Section 3.4).

5 Discussion

Replication studies are becoming more and more popular and encouraged in many domains of science. However, the existing literature greatly focuses on superiority studies, and non-significant studies are often incorrectly interpreted as showing evidence for a null effect. In order to bridge this gap, we proposed two methods for the analysis and the design of replication studies with an equivalence design: the two-trials rule and the sceptical TOST procedure.

Both approaches exactly control the overall T1E rate at level \(\alpha^2\) if the replication sample size is suffi-
Figure 6: Relative sample size $c$ to reach a conditional or predictive power of 80% (top) and conditional TIE with a conditional power of 80% (bottom) of the sceptical TOST procedure and the two-trials rule as a function of $p_o^+$ for $f_o = 0.1$ and $f_o = 0.9$. The top axis in the bottom plot shows the required relative sample size $c$ with $f_o = 0.1$ (first row) and $f_o = 0.9$ (second row) to reach a conditional power of 80%.
ciently large. The main difference between the two approaches is that replication success is possible with the sceptical TOST procedure if one of the $p$-values is non-significant, but not with the two-trials rule. As a result, the sceptical TOST procedure has a larger project power than the two-trials rule. This increase in project power comes at the price of an increased partial TIE rate. However, the conditional TIE rate of the sceptical TOST procedure is smaller than the one of the two-trials rule for larger values of $p^+_o$, and is at most less than two times larger otherwise, which is considered acceptable by some authors (Rosenkranz 2002). In addition, sample size calculation is possible even for original studies with $p^o_{max} > \alpha$ with the sceptical TOST procedure. However, one might argue that the bound $\gamma_c$ on the partial TIE rate becomes unreasonably large if $c$ is very large. To mitigate this issue, an alternative would be to use a method with partial TIE rate not depending on $c$, such as Edgington’s method (Held et al. 2024).

Some limitations need to be noted. Our methodology relies on normality of the effect estimates, which might seem restrictive. However many framework fall into this category after a suitable transformation. It also needs to be noted that two study pairs from Errington et al. (2021) are for illustrative purposes only, and the results depend on the choice of the margin. A sensitivity analysis could be performed by looking at $p^{max}$ and $p^{o_{max}}$ as a function of the margin (Hauck and Anderson 1986).

Future work will focus on developing a sceptical confidence interval using the $p$-value function (Infanger and Schmidt-Trucksäss 2019). Replication success could then be assessed by verifying whether the sceptical confidence interval is contained within the equivalence region.

**Data and software availability**

The dataset used in this paper has been downloaded from https://osf.io/39s7j (Errington and Denis 2021). The code to reproduce all the analyses and figures can be found at https://gitlab.uzh.ch/charlotte.micheloud/repromat-equivalence, together with the R-package RepEquivalence which contains functions for the design and analysis of replication studies with an equivalence design.

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Conflict of interest

The authors have no conflict of interest to declare.

Appendix

A Success region for $z_r^+$

Two-trials rule The condition on $z_r^+$ for replication success is $z_r^+ < -z_\alpha$, and the condition on $z_r^-$ is $z_r^- > z_\alpha$. Moreover, $z_r^-$ can also be expressed as

$$z_r^- = (\hat{\theta}_r + \delta)/\sigma_r = z_r^+ + \frac{2z_o^+\sqrt{c}}{f_o - 1},$$

so the success region for $z_r^+$ is

$$z_\alpha - \frac{2z_o^+\sqrt{c}}{f_o - 1} < z_r^+ < -z_\alpha$$

Sceptical TOST procedure Following Micheloud et al. (2023, Equation (16)) with $z_o = z_o^+$ and $z_r = z_r^+$, the condition on $z_r^+$ for replication success with the sceptical TOST procedure is

$$z_r^+ < -z_\gamma \sqrt{1 + c/(K_o^+ - 1)},$$

and similarly, the condition on $z_r^-$ is

$$z_r^- > z_\gamma \sqrt{1 + c/(K_o^- - 1)}.$$  

Now, using (3) and (15), Equation (17) can be rewritten as

$$z_r^+ > z_\gamma \sqrt{1 + c/\left\{ \frac{(f_o + 1)^2}{(f_o - 1)^2} K_o^+ - 1 \right\}} - \frac{2z_o^+\sqrt{c}}{f_o - 1}.$$  

Putting (16) and (18) together gives the success region for $z_r^+$. 

20
B Success region for $z_o^+$

**Two-trials rule** The condition on $z_o^+$ for replication success is $z_o^+ < -z_\alpha$, and the condition on $z_o^-$ is $z_o^- > z_\alpha$. Moreover, $z_o^-$ can also be expressed as

$$z_o^- = \frac{\hat{\theta}_o + \delta}{\sigma_o} = z_o^+ + \frac{2z_r^+}{\sqrt{c(f_r - 1)}},$$

(19)

so the success region for $z_o^+$ is

$$z_\alpha - \frac{2z_r^+}{(f_r - 1)\sqrt{c}} < z_o^+ < -z_\alpha.$$

**Sceptical TOST procedure** Equations (16) and (17) are rearranged to give a condition on $z_o^-$ and $z_o^+$, respectively. Using (3) and (19), the success region of $z_o^+$ is

$$z_\gamma \sqrt{1 + \frac{c}{(K_r - 1)}} - \frac{2z_r^+}{(f_r - 1)\sqrt{c}} < z_o^+ < -z_\gamma \sqrt{1 + \frac{c}{(K_r + 1)}}.$$

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