Non-Inferiority Test for a Continuous Variable with a Flexible Margin in an Active Controlled Trial : An Application to the "Stratall ANRS 12110 / ESTHER" Trial

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Research

Keywords: Asymptotic test, Active controlled trial, Confidence interval, Flexible margin, Non-inferiority

Posted Date: June 25th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-21325/v3

Version of Record: A version of this preprint was published at Trials on March 5th, 2022. See the published version at https://doi.org/10.1186/s13063-022-06118-x.

RESEARCH

Non-inferiority test for a continuous variable with a flexible margin in an active controlled trial : An application to the "Stratall ANRS 12110 / ESTHER" trial

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Abstract

Background: Non-inferiority trials are becoming increasingly popular in public health and clinical research. The choice of the non-inferiority margin is the cornerstone of such trials. Most of the time, the non-inferiority margin is fixed and constant, determined from historical trials as a fraction of the effect of the reference intervention. But in some circumstances, the effect of the reference intervention may be unknown. In this case, the non-inferiority margin is not fixed in advanced and depends on the reference intervention estimate. Hence, the uncertainty surrounding the non-inferiority margin should be accounted for in statistical tests. In this work, we explore how to perform the non-inferiority test for a continuous variable with a flexible margin.

Methods: We have proposed in this study, two procedures for the non-inferiority test with a flexible margin for continuous endpoints. The proposed test procedures are based on a test statistic and confidence interval approaches respectively. Simulations have been used to assess the performances and properties of the proposed test procedures. An application was done on a clinical real data, to assess the efficacy of clinical monitoring alone versus laboratory and clinical monitoring in HIV-infected adult patients.

Results: Basically, for both proposed methods, the type I error estimate was not dependent on the values of the reference treatment. In the test statistic approach, the type 1 error rate estimate was approximatively equal to the nominal value. It has been found that the confidence interval level determined approximatively the level of significance. For a given nominal type I error α, the appropriate one- and two-sided confidence intervals should be with levels $1-\alpha$ and $1-2\alpha$ respectively.

Conclusions: Based on type I error rate and power estimates, the proposed non-inferiority hypothesis test procedures had good performances and were applicable in practice.

Trial registration: The trial data used in this study was from the "Stratall ANRS 12110 / ESTHER", registered with ClinicalTrials.gov, number NCT00301561. Date : March 13, 2006, url : https://clinicaltrials.gov/ct2/show/NCT00301561.

Keywords: Asymptotic test; Active controlled trial; Confidence interval; Flexible margin; Non-inferiority

1 Background

After developing a new health intervention (treatment or diagnostic test), the next step is to assess its effectiveness, relatively to the existing reference intervention. There are several strategies to do this, such as the superiority trials which involves testing whether the new treatment is superior to another (placebo, reference or active control treatment). However, when the active control intervention achieves maximum efficacy or the use of a placebo is unethical, it becomes difficult to statistically show the superiority of the new health intervention. Studies aimed at showing that a new intervention is not worse than the active control intervention of more than a pre-specified amount of efficacy have become increasingly common in the recent decade [1]. The expression *'is not worse than the active control intervention of more than a pre-specified amount'*, means it is acceptable to lose a 'little bit' of the main effect of the active control intervention compared to a new intervention's benefits (fewer side effects, costs, tolerable and safer). This acceptable loss of efficacy

refered to as the *non-inferiority margin*. A trial showing that the new intervention is *non-inferior* to the active control intervention is called *A non-inferiority trial* [1].

The Food and Drug Administration(FDA)[2] provided general principles for an appropriate choice of the non-inferiority margin. The non-inferiority margin is at the upper limit of the confidence interval, so the trial is designed to show evidence of no more than this 'loss of maximum efficacy'. Generally, this margin is fixed, determined from historical trials as a fraction of the treatment effect. However, in some cases, there may exist no historical trials and the margin in such cases should be non-fixed and dependent on the reference treatment effect estimate. For binary endpoints, tests that account for non-fixed margins have been studied [3, 4, 5]. One finds that most works on the non-inferiority test for continuous endpoints with fixed and linear margin have been focused on the confidence intervals approach [6, 7, 8], mainly consisting of comparing the bounds of the treatments difference to the fixed margin. However, few studies have been performed for a non-fixed or variable margin for continuous endpoints. This work is aimed of deriving non-inferiority tests for continuous endpoints with flexible margin in active randomized controlled trials. An application of the proposed methods is done on the Stratall ANRS 12110/ESTHER trial.

2 Methods

2.1 Notations

Definition of the basic notations used.

- X_R and X_N, the random variables for continuous primary endpoint in the active control group and new intervention group (new group) respectively.
- n_R and n_N, the sample sizes for the active control group and new group respectively .
- μ_R and μ_N, the means of continuous primary endpoint for the active group and new group respectively.
- σ_R^2 and σ_N^2, the variances of continuous primary endpoint for the active group and new group respectively.
- $\Delta_L(\mu_R)$ is the non-inferiority margin, and $\Delta = \mu_N - \mu_R$ the difference of true means.
- H_0 and H_1 are the null and alternative hypotheses respectively.

2.2 Approach using a test statistic

Without loss of generality, assuming that an increase in the endpoint corresponds to more efficacy. The non-inferiority hypotheses can be formulated as follows:

$$\begin{cases} H_0 : \mu_N \leq \mu_R - \Delta_L & \textit{There is no non-inferiority} \\ H_1 : \mu_N > \mu_R - \Delta_L & \textit{There is non-inferiority} \end{cases} \tag{1}$$

The formulation of the hypotheses test in equation (1) shows that the acceptance of the non-inferiority means that the new intervention is not worse than the active control intervention with a Δ_L margin. When Δ_L is fixed, testing the hypotheses (1) can be viewed as a classical composite hypotheses test for mean difference [9],

therefore, based on the central limit theorem applied to the boundary of the null hypothesis, the asymptotic test Z_{fixed} can be obtained by:

$$Z_{fixed} = \frac{\bar{X}_N - \bar{X}_R + \Delta_L}{\sqrt{\frac{\sigma_N^2}{n_N} + \frac{\sigma_R^2}{n_R}}} \sim N(0,1). \tag{2}$$

In effect, when Δ_L is fixed, we have :

$$\begin{aligned} Var(\bar{X}_N - \bar{X}_R + \Delta_L) &= Var(\bar{X}_N) + Var(\bar{X}_R) \\ &= \frac{\sigma_N^2}{n_N} + \frac{\sigma_R^2}{n_R}. \end{aligned} \tag{3}$$

The null hypothesis is rejected if $Z_{fixed} > Z_{1-\alpha}$, where $Z_{1-\alpha}$ is the $(1-\alpha)$ percentile of the standard normal distribution. From the Karlin-Rubin theorem, this test is the uniformly most powerful test of level α [10].

If Δ_L is not fixed, i.e, if Δ_L is a function of μ_R, then, $Var\{\bar{X}_N - \bar{X}_R + \Delta_L(\bar{X}_R)\} \neq Var(\bar{X}_N) + Var(\bar{X}_R)$, and therefore $Var(\bar{X}_N) + Var(\bar{X}_R)$ is not a valid variance of $\bar{X}_N - \bar{X}_R + \Delta_L(\bar{X}_R)$. Under the assumption that Δ_L is continuously differentiable function, variance estimation was performed using Delta method discussed below.

2.2.1 Variance estimation using Delta method

If $\Delta_L(.)$ is continuously differentiable such that $\Delta'_L(\mu_R) \neq 0$ (Δ'_L is the first derivative of Δ_L), then, using the Taylor series of order 1 in a neighborhood of μ_R,

$$\Delta_L(\bar{X}_R) = \Delta_L(\mu_R) + \Delta'_L(\mu_R)(\bar{X}_R - \mu_R) + o_p(1). \tag{4}$$

Hence,

$$\begin{aligned} &\{\bar{X}_N - \bar{X}_R + \Delta_L(\bar{X}_R)\} - \{\mu_N - \mu_R + \Delta_L(\mu_R)\} \\ &= (\bar{X}_N - \mu_N) - (\bar{X}_R - \mu_R) + \{\Delta_L(\bar{X}_R) - \Delta_L(\mu_R)\} \\ &= (\bar{X}_N - \mu_N) - (\bar{X}_R - \mu_R) + \Delta'_L(\mu_R)(\bar{X}_R - \mu_R) + o_p(1) \\ &= (\bar{X}_N - \mu_N) + \{\Delta'_L(\mu_R) - 1\}(\bar{X}_R - \mu_R) + o_p(1) \end{aligned}$$

Thus, the variance estimate is :

$$Var\{\bar{X}_N - \bar{X}_R + \Delta_L(\bar{X}_R)\} = \frac{\sigma_N^2}{n_N} + \frac{\{\Delta'_L(\mu_R) - 1\}^2 \sigma_R^2}{n_R} \tag{5}$$

The test statistic can then be expressed as :

$$Z_{flexible} = \frac{\{\bar{X}_N - \bar{X}_R + \Delta_L(\bar{X}_R)\} - \{\mu_N - \mu_R + \Delta_L(\mu_R)\}}{\sqrt{\frac{\sigma_N^2}{n_N} + \frac{\{\Delta'_L(\mu_R) - 1\}^2 \sigma_R^2}{n_R}}}. \tag{6}$$

2.2.2 Asymptotic properties of the test statistic $Z_{flexible}$.
From the central limit theorem, when n_N and n_R approach infinity , the random variable $Z_{flexible} \sim N(0,1)$ on the boundary of null hypothesis, that is, asymptotically,

$$Z_{flexible} = \frac{\bar{X}_N - \bar{X}_R + \Delta_L(\bar{X}_R)}{\sqrt{\frac{\sigma_N^2}{n_N} + \frac{\{\Delta'_L(\mu_R)-1\}^2\sigma_R^2}{n_R}}} \sim N(0,1). \tag{7}$$

μ_R is unknown and σ_R^2 and σ_N^2 may be unknowns, which need to be estimated. We used the maximum likelihood estimation method on the boundary of the null hypothesis ($\mu_N = \mu_R - \Delta_L(\mu_R)$). The unknown parameters are estimated considering the cases where the variances σ_R^2 and σ_N^2 are known, unknown, equal or unequal.

The maximum likelihood(ML) estimators $\hat{\mu_R}$, $\hat{\sigma_R}^2$ and $\hat{\sigma_N}^2$ for μ_R, σ_R^2 and σ_N^2 respectively are consistent. Moreover, since Δ'_L is assumed continuous, $\Delta'_L(\hat{\mu_R})$ is a consistent estimator for $\Delta'_L(\mu_R)$. The estimator $\hat{Z}_{flexible}$ of the test statistic $Z_{flexible}$ can be obtained by replacing the unknown parameters in (6) by their ML estimators. Therefore, the test H'_0 versus H_1(where H'_0 is the boundary of H_0 i.e $\mu_N = \mu_R - \Delta_L(\mu_R)$), is rejected if $\hat{Z}_{flexible} > z_{1-\alpha}$, where α is the nominal type I error and $z_{1-\alpha}$ denotes the $1-\alpha$ percentile of the standard normal distribution. The significance level of this test tends to α when n_N and n_R approach infinity.

Assuming that, under alternative hypotheses H_1, $\mu_N - \mu_R + \Delta_L(\mu_R) = v$, we have $v > 0$. Hence, if η is the power of the test, it follows that:

$$\begin{aligned}
\eta &= \mathbf{P}\Big(\frac{\bar{X}_N - \bar{X}_R + \Delta_L(\bar{X}_R)}{\sqrt{\frac{\sigma_N^2}{n_N} + \frac{(\Delta'_L(\mu_R)-1)^2\sigma_R^2}{n_R}}} > z_{1-\alpha}/H_1\Big) \\
&= \mathbf{P}\Big(\frac{\bar{X}_N - \bar{X}_R + \Delta_L(\bar{X}_R) - v}{\sqrt{\frac{\sigma_N^2}{n_N} + \frac{(\Delta'_L(\mu_R)-1)^2\sigma_R^2}{n_R}}} > \\
&z_{1-\alpha} - \frac{v}{\sqrt{\frac{\sigma_N^2}{n_N} + \frac{(\Delta'_L(\mu_R)-1)^2\sigma_R^2}{n_R}}}\Big),
\end{aligned}$$

where, under alternative hypothesis, $\frac{\bar{X}_N - \bar{X}_R + \Delta_L(\bar{X}_R) - v}{\sqrt{\frac{\sigma_N^2}{n_N} + \frac{(\Delta'_L(\mu_R)-1)^2\sigma_R^2}{n_R}}} \sim N(0,1)$. Thus, the power, given as a function of v, n_N, n_R and α is:

$$\eta(v, n_N, n_R) = \Phi\Big(\frac{v}{\sqrt{\frac{\sigma_N^2}{n_N} + \frac{(\Delta'_L(\mu_R)-1)^2\sigma_R^2}{n_R}}} - z_{1-\alpha}\Big), \tag{8}$$

where Φ is the cumulative distribution function of the standard normal distribution. For a fixed nominal type I error α, and for any fixed μ_R and μ_N such that $v = \mu_N - \mu_R + \Delta_L(\mu_R) > 0$, when $n_R \to \infty$ and $n_N \to \infty$, it follows that $\eta \to 1$. Therefore, the test $Z_{flexible}$ is asymptotically convergent. From equation 8, it is possible to find the sample size that achieves the nominal fixed power. Denoting the nominal type II error by β and assuming that $n_N = rn_R$ with $r > 1$, the sample size which will allow nominal power $(1-\beta)$ is such that:

$$n_R \geq \frac{(z_{1-\alpha} + z_{1-\beta})^2[\sigma_N^2 + r\sigma_R^2\{\Delta'_L(\mu_R) - 1\}^2]}{rv^2}. \tag{9}$$

This formula is equivalent to the one found in [9] when the margin is fixed.

The proposed test statistic $\hat{Z}_{flexible}$ is asymptotic, hence, works well for large sample sizes, hence not adapted for datasets with small sample sizes, which are not uncommon in pratical situations.In such cases, the non-parametric test based on the percentile bootstrap confidence interval can be used[11]. The latter, which does not require any assumptions on the sample size or sample distribution.

2.3 Approach based on confidence intervals

For any test based on confidence interval, the main interest is on the level of confidence intervals which is required to achieve a desired nominal type I error. Moreover, as discussed in [9] and [12], the type I error is a controversial issue in clinical trial tests. In the framework of non-inferiority tests, when the non-inferiority margin is fixed, [13] recommended using $1-\alpha$ and $1-\frac{\alpha}{2}$ for two sided and one sided confidence interval levels respectively, while [7] recommended to use $1-2\alpha$ for two sided and $1-\alpha$ for one sided confidence intervals. In [7], it is argued that the recommendation of [13] would lead to a conservative test, as the estimate type I error rate would be half the nominal one. Moreover, it has been argued that there would be approximately a 10% loss of power. In this section, we propose a non-parametric procedure for the confidence interval(one-sided and two sided) construction when the non-inferiority margin is flexible.

An intuitive procedure based on confidence intervals for the hypotheses test in equation (1) would be by checking the overlapping of the confidence intervals of $\mu_N-\mu_R$ and $-\Delta_L(\mu_R)$. The null hypothesis would be rejected if the two confidence intervals are non-overlapped, and not rejected otherwise. In such case, as illustrated in [14], the intervals may be overlapped while the statistics would not be necessarily non significantly different, thus, the power of the test would be lower. The proposed procedure involves comparing the lower bound of the confidence interval(one- or two-sided respectively) with γ% level of $\mu_N-\mu_R+\Delta_L(\mu_R)$ with 0. The null hypothesis H_0 is rejected if the lower bound of the confidence interval for $\mu_N-\mu_R+\Delta_L(\mu_R)$ is greater than 0.

Estimation of the type I error is performed using simulations and non-parametric estimation of confidence intervals on the boundary of the null hypothesis. The detailed steps are described below.

1. From a fixed μ_R, calculate $\mu_N = \mu_R - \Delta_L(\mu_R)$ (satisfying the null hypothesis H_0). We assume that the standard deviations σ_N and σ_R are respectively known.
2. Let m denote the number of desired simulations, for $i \in \{1\cdots m\}$, simulate m pairs of samples X_N and X_R of size n_N and n_R respectively from the normal distribution $\mathcal{N}(\mu_N,\sigma_N)$ and $\mathcal{N}(\mu_R,\sigma_R)$ respectively.
3. Using bootstrap, compute the empirical percentile confidence intervals $[a_i,\infty]$ for one-sided confidence interval (and $[a_i,b_i]$ for two-sided confidence interval respectively) of level γ for $\mu_N-\mu_R+\Delta_L(\mu_R)$, for $i\in\{1\cdots m\}$.
4. For $i\in\{1\cdots m\}$ H_0 is rejected when $a_i>0$, thus the level of significance is estimated by : $\alpha(\gamma)=\dfrac{1}{m}\sum_{i=1}^{m}1_{a_i>0}$.

Like any other power estimation, the data are drawn under the alternative hypothesis that is, $\mu_N > \mu_R-\Delta_L(\mu_R)$. Since there is a wide range of possibilities

on the alternative hypothesis, in practice, one considers the equivalence point, that is, $\mu_R = \mu_N$. Therefore, similarly to studies of [5] and [15], the equivalence point ($\mu_R = \mu_N$) will be used for drawing data for the power estimation.

1. Given μ_R, simulate m pairs of samples X_N and X_R of respective sizes n_N and n_R using the resspective normal distributions $\mathcal{N}(\mu_R, \sigma_N)$ and $\mathcal{N}(\mu_R, \sigma_R)$.

2. Using bootstrap, compute the empirical percentile confidence intervals $[a_i, b_i]$ of level γ for $\mu_N - \mu_R + \Delta_L(\mu_R)$, for $i \in \{1 \cdots m\}$.

3. For $i \in \{1 \cdots m\}$ H_0 is rejected when $a_i > 0$. Thus the power is estimated by, $\eta(\gamma) = \frac{1}{m} \sum_{i=1}^{m} 1_{a_i > 0}$.

2.4 Performances assessment

Simulations were done to evaluate the finite-sample performances of the asymptotic test and confidence interval based test. The performance indicators used were the type I error and statistical power. Monte-Carlo simulation techniques were used for the estimation of the considered indicators. In the simulations, we considered the linear margin $\Delta_L(\mu_R) = 0.25 * \mu_R$; equal and known variances $\sigma^2 = \sigma_R^2 = \sigma_N^2$, $\sigma^2 = 1$; .

Both indicators were computed for the two proposed tests according to the reference treatment. For the type I error, data were drawn on the boundary of the null hypothesis: for a given μ_R, μ_N is obtained such that $\mu_N = \mu_R - \Delta_L(\mu_R)$. For the power, data were drawn under the alternative hypothesis: for a given μ_R, μ_N is obtained such that $\mu_N > \mu_R - \Delta_L(\mu_R)$. Usually, one takes $\mu_N = \mu_R$. In all cases, it is assumed that μ_R vary in $[1, 1000]$.

In the approach based on the asymptotic test, the nominal type I error was fixed and set at $\alpha = 5\%$. For the confidence interval based test, we considered 95% one- and two-sided confidence interval levels. The purpose was to estimate the type I error rate for the respective confidence interval. In all the simulations, we considered balanced sample sizes (that is when $n = n_N = n_R$), $n = 20, 100$ and 1000 for small, medium and large sample sizes respectively. The number of bootstrap samples with replacement was $B = 1000$ and the number of simulation replications was $m = 10000$. The **R** software programming language [16] was used to conduct the simulations and codes are accessible in a separate file on request.

2.5 Application to the Stratall ANRS 12110 / ESTHER

This study was motivated by the randomised and non-inferiority "Stratall ANRS 12110 / ESTHER" trial [17]. The main purpose was to assess an exclusively clinical monitoring strategy compared with a clinical monitoring strategy plus laboratory monitoring in terms of effectiveness and safety in HIV-infected patients in Cameroon. The idea was to achieve the scaling-up of HIV care in rural districts where most people live with HIV, but local health facilities generally have the low-grade equipment. A total of 459 HIV infected patients were included in the study and randomly allocated to two groups, one receiving exclusively clinical monitoring (Intervention group, N=238) and the other receiving Laboratory and clinical monitoring (active control group, N=221). All patients included were initiated antiretroviral treatment and were followed up for 24 months. Clinical monitoring alone was compared to laboratory and clinical monitoring in a non-inferiority design. The

continuous primary endpoint was the increase in CD4 cells count from treatment initiation to the twenty-fourth month. Based on previous studies, the non-inferiority margin ($\Delta_L(R)$) was prespecified as a linear function (25 %) of mean CD4 cells increase (μ_R) after 24 months of antiretroviral treatment in laboratory and clinical monitoring group , $\Delta_L(R) = \frac{25}{100}\mu_R$. Unlike other non-inferiority studies [18, 19], non-inferiority margin in this study was varied (depending on the mean increase in CD4 in the active control group). However, the classical two-sided confidence interval based test with 90% level were used to obtain a type I error (α) close to 5% [17]. Indeed, the statistical test procedures that explore the non-inferiority test for continuous data with variable margin were not available. Moreover, as discussed in [12], the relationship between the confidence intervals level and the type I error can be controversial.

More details about the background of the study and the clinical trial process can be found in [17]. Two analyses were done according to the type of data :

1 Firstly, the increase of CD4 cells count at 24 months from the baseline was considered, which implies missing or lost patients before the end of follow-up period were excluded in the analysis. In that case, the total number of patient in the analysis reduced to $n = 334$, with $n_R = 169$ and $n_N = 165$. "Observed data" will refer to the case where data are analyzed by excluding participants with missing observation at 24 months.

2 Secondly, an analysis was done with all participants who attended at least one follow-up visit, and the last observation carried forward (LOCF) imputation method was applied for participants whose CD4 data were missing at 24 months.

The classical parametric two-sided confidence interval based test with 90% level was used by [17] to perform the non-inferiority test. The final result was that the CLIN was not non-inferior to the LAB.

3 Results

3.1 Simulations results

3.1.1 Test statistic based test

Results for the approach based on a statistic are summarized in the figures 1 and 2 for type I error rate and power estimates respectively. Whatever the sample size, it is observed that the type I error rate estimates were constant and were not μ_R dependent. For small sample size, the type I error rate estimate was slightly above the nominal value, while the median value estimate was 0.053, and an Interquartile Range(IQR) of $[0.051 - 0.054]$. As the sample size increases, the type I error estimates get closer to the nominal value. In effect, for medium sample size of $n = 100$, the type I error estimate is closer to the nominal value, the median value estimate for μ_R was 0.05 ($IQR = [0.051 - 0.052]$). For large sample sizes, for example, $n = 500$, the type I error estimate was more accurate and closest to the nominal value, the median estimate was 0.05 ($IQR = [0.0501 - 0.0503]$). Concerning the power estimates, Excepted at the neighborhood of 1 for small and medium sample sizes 20 and 100 respectively, the power rate was almost 100% whatever the value of μ_R.

3.1.2 Confidence interval based test

The results for the approach based on confidence intervals are summarized in Figures 3, 4, 5 and 6. For 95% both one- and two-sided confidence intervals level, the estimate type I error rates remained around 0.05 and 0.025 respectively and are more concentrated around those values as the sample sizes get larger. Then, for a given nominal type I error of α, the suitable confidence intervals level would be $1-\alpha$ and $1-2\alpha$ for one- and two-sided confidence intervals respectively. The power(at the equivalence point, $\mu_R = \mu_N$) converged to 1 for all values of μ_R, excepted for small sample sizes where for small values of μ_R at the neighborhoud of 1.

3.2 The Stratall ANRS 12110 / ESTHER trial

The proposed methods were also applied to the Stratall ANRS 12110 / ESTHER tria, based on Observer and LOCF data, with a linear margin of $\Delta_L(R) = \frac{25}{100}R$. The results for the approach based on the test statistic are summarized in the table 1. The p-value is calculated based on the test statistic in equation (6). The statistical power was computed using equation (8) and based on the same inputs as in [17], which were $\mu_N = \mu_R = 140$ and $\sigma_N = \sigma_R = 130$. For the Observed data, the p-value estimate was = 0.02, and the null hypothesis that CLIN is not non-inferior to the LAB is rejected at 0.05 level. On the other hand, for the LOCF data, the p-value was = 0.09 and the null hypothesis that CLIN is not non-inferior to the LAB was not rejected at 0.05 level.

For the confidence intervals based approach, the test was performed by considering the one- and two-sided confidence interval levels respectively. The results are presented in the Table 2. The null hypothesis that CLIN was not non-inferior to LAB is rejected for any of the confidence intervals used. Basically, the obtained results are in line with those in [17] : the clinical monitoring alone was not non-inferior to laboratory plus clinical monitoring.

4 Discussions

In this study, we have proposed two non-inferiority test approaches for a continuous endpoints with flexible margins: a test based on a test statistic and a confidence interval based test. Confidence interval approach is more used in literature and recommended by the international guideline [2]. For the non-inferiority test with continuous endpoints and fixed margin, some studies like [7] and [12] studied the confidence interval approach which does not allowed for explicit sample size calculation. Comparatively, our proposed test based on a statistic allows explicit calculation of sample size and power formula.

The simulation results for the confidence intervals based test showed that the confidence interval level determined approximatively the type I error rate. The test with 95% one- and two-sided confidence intervals level led to type I errors which were approximated by 0.05 and 0.025 respectively. Therefore, for a given nominal type I error $\alpha = 0.05$, the confidence intervals based test would be performed with one- or two-sided confidence intervals with $1-\alpha$ or $1-2\alpha$ levels respectively, these findings are consistent with those in [7]. However, [13] recommended the use of one- or two-sided confidence intervals with levels $1-\alpha/2$ or $1-\alpha$ respectively. As

argued in [12], this latter approach would necessarily lead to a conservative test. In fact, the non-inferiority hypothesis test is a one-tailed test, so, when performing the testing procedure with the classical nominal type I error α, the actual type I error would be $\alpha/2$. Therefore, for a given desired nominal type I error, to avoid the conservativeness of the test, the test should be performed with this nominal error times two. However, the debate on which of the one- or two-sided confidence intervals should be used in non-inferiority trials remains open, which is discussed in [20].

The most important output of this study was the type I error which was not varying according to the value of reference treatment, either for the test based on a statistic or the test based on confidence intervals. This suggested that the variability and uncertainty around the margin were accounted for, without affecting the properties of the proposed tests. The proposed methods in this study could therefore be viewed as a generalization of the case where the non-inferiority margin is fixed for continuous endpoints. The weakness of the power observed at the neighborhood of 1 may be due to the fact that for small and little values of the reference treatment, the associated margin would be small and closer to 0(for e.g, if $\mu_R = 1$, then, considering the Δ_L define in our simulation scenario, $\Delta_L(\mu_R) = 0.25$), and in this case, the null hypothesis is more likely to be realized than the alternative $\mu_R = \mu_N$. Therefore, the proposed methods for outcomes on small scales should be used cautiously especially for small sizes.

5 Conclusions

In an active-controlled trial of non-inferiority, the non-inferiority margin should be a function of reference treatment. This paper produced a framework on how to perform the non-inferiority hypothesis test with a flexible margin. Based on type I one error rate and power estimates, the proposed non-inferiority hypothesis test procedures have good performances and are applicable in practice, a practical application on real clinical data was illustrative.

Abbreviations

CD4: Cluster of Differentiation 4; CLIN: Clinical monitoring alone; HIV/AIDS: Human immunodeficiency virus infection and acquired immune deficiency syndrome; LAB: Laboratory and clinical monitoring; LOCF : Last Observation Carried Forward.

Acknowledgements

ABS is grateful to the African Union, he was a recipient of a full scholarship for his doctoral studies.

Authors' contributions

ABS and JBTM drafted the manuscript, proposed methods and analyzed the data. NM, CK and CL produced real clinical data, read and edited the manuscript, and provided observations. AW read, edited the manuscript and provided observations.

Funding

No funding was obtained for this study.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author or the or the author named Christian Laurent (christian.laurent@ird.fr) on reasonable request.

Ethics approval and consent to participate

This study involved an analysis of data that was already analyzed in a primary research work. A confidential agreement was done with the main investigators.

Consent for publication

Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Figures

Figure 1 Type I error rate estimates according to sample sizes for test statistic based test
Type I error rate estimates as function of reference treatment, for the test statistic based test from From the left to the rigth, sample sizes are $n_N = n_R = 20$, 100 and 1000 respectively.

Figure 2 Power estimates according to sample sizes for test statistic based test
Power estimates as function of reference treatment, for test statistic based test. From the left to the rigth, sample sizes are $n_N = n_R = 20$, 100 and 1000 respectively.

Tables

Figure 3 Type I error rate estimates according to sample sizes for the 95% one-sided confidence intervals level based test
Type I error rate estimate as function of reference treatment, for the 95% one-sided confidence intervals level based test. From the left to the rigth, sample sizes are $n_N = n_R = 20$, 100 and 1000.

Figure 4 Power estimates according to sample sizes for the 95% one-sided confidence intervals level based test
Power estimates as function of reference treatment, for the 95% one-sided confidence intervals level based test. From the left to the rigth, sample sizes are $n_N = n_R = 20$, 100 and 1000.

Figure 5 Type I error rate estimates according to sample sizes for the 95% two-sided confidence intervals level based test
Type I error rate estimate as function of reference treatment, for the 95% two-sided confidence intervals level based test. From the left to the rigth, sample sizes are $n_N = n_R = 20$, 100 and 1000.

Figure 6 Power estimates according to sample sizes for the 95% two-sided confidence intervals level based test
Power estimates as function of reference treatment, for the 95% two-sided confidence intervals level based test. From the left to the rigth, sample sizes are $n_N = n_R = 20$, 100 and 1000.

Table 1 P-value and power determination for the approach based on the asymptotic test statistic and according to the data used

	$p-value$	$Power$
Case of LOCF	0.02	0.77
Case of observed data	0.11	0.82

Table 2 Confidence interval calculations and decision on non-inferiority confidence interval based test

	One-sided CI	Two-sided CI
	Case of LOCF	
$CLIN - LAB + \Delta_L(LAB)$	-5 to 47	-10 to 52
Decision	No non-inferiority	No non-inferiority
	Case of observed data	
$CLIN - LAB + \Delta_L(LAB)$	7 to 67	1 to 72
Decision	Non-inferiority	Non-inferiority

Figures

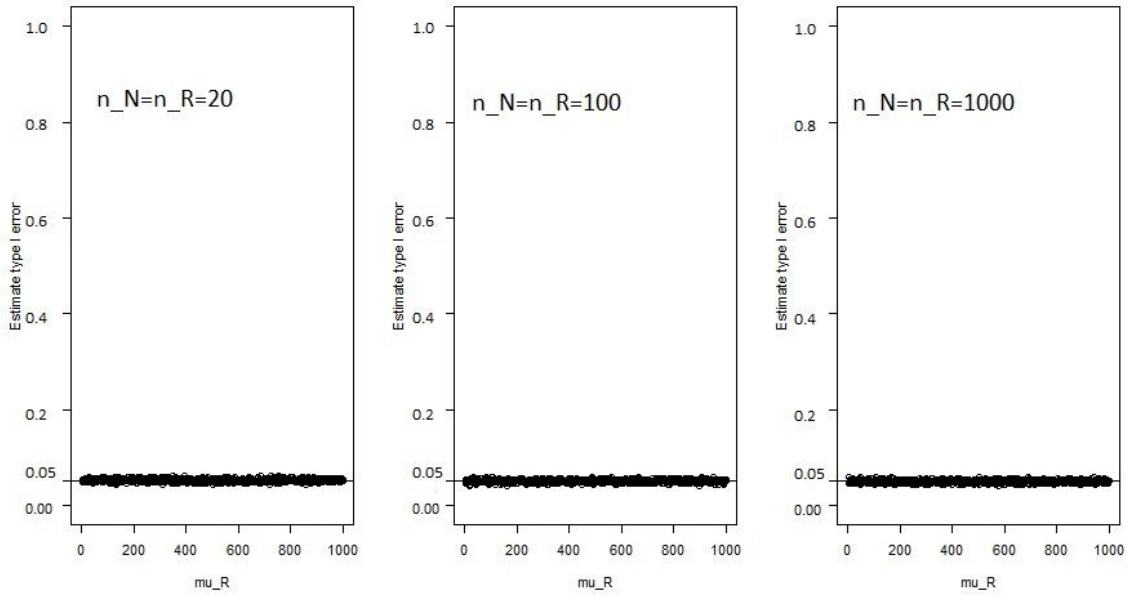


Figure 1

Type I error rate estimates according to sample sizes for test statistic based test Type I error rate estimates as function of reference treatment, for the test statistic based test from From the left to the rigth, sample sizes are nN = nR = 20, 100 and 1000 respectively.

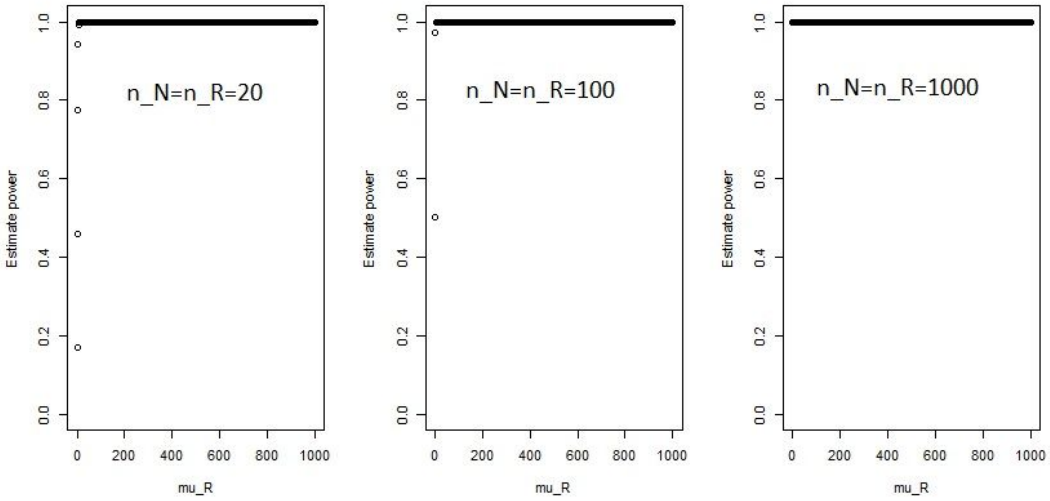


Figure 2

Power estimates according to sample sizes for test statistic based test Power estimates as function of reference treatment, for test statistic based test. From the left to the rigth, sample sizes are nN = nR = 20, 100 and 1000 respectively.

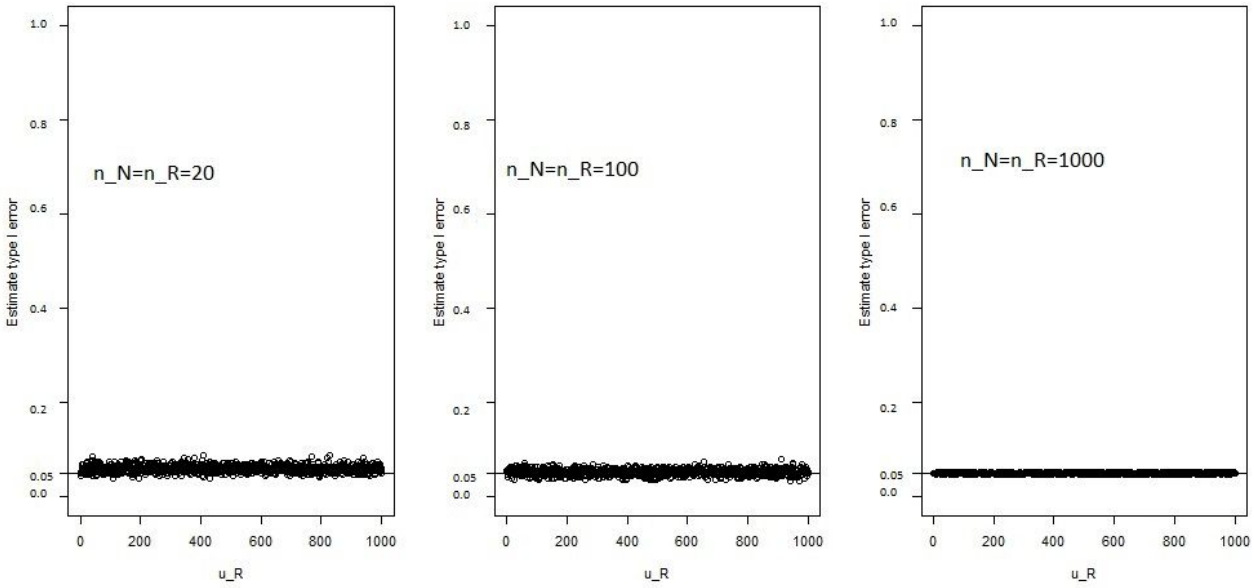
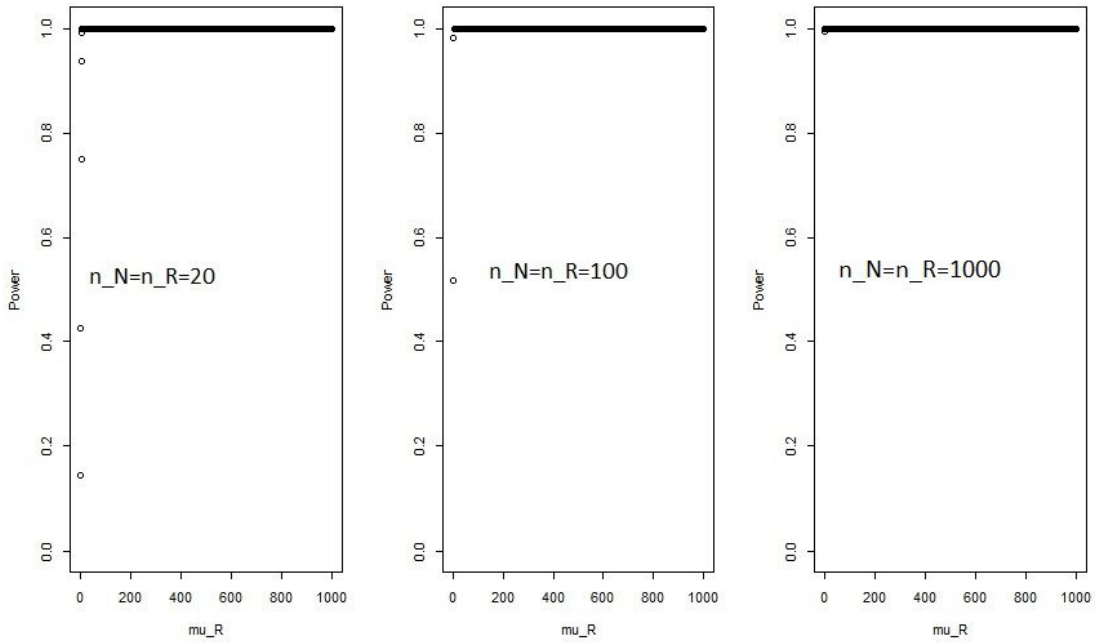


Figure 3

Type I error rate estimates according to sample sizes for the 95% one-sided confidence intervals level based test Type I error rate estimate as function of reference treatment, for the 95% one-sided confidence intervals level based test. From the left to the rigth, sample sizes are nN = nR = 20, 100 and 1000.



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Power estimates according to sample sizes for the 95% one-sided confidence intervals level based test
Power estimates as function of reference treatment, for the 95% one-sided confidence intervals level based test. From the left to the rigth, sample sizes are nN = nR = 20, 100 and 1000.

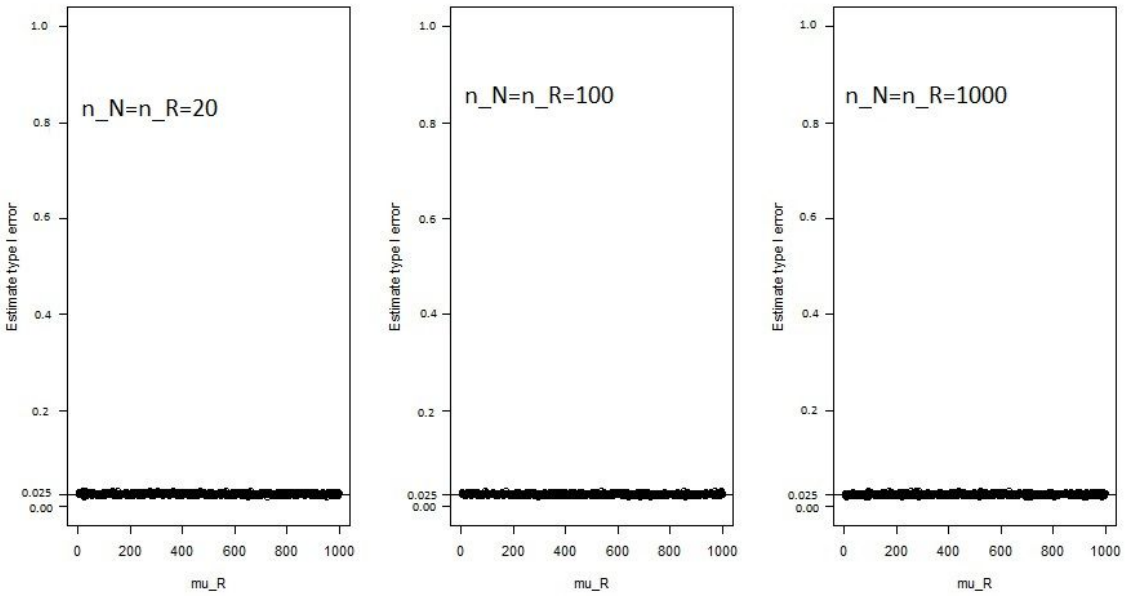
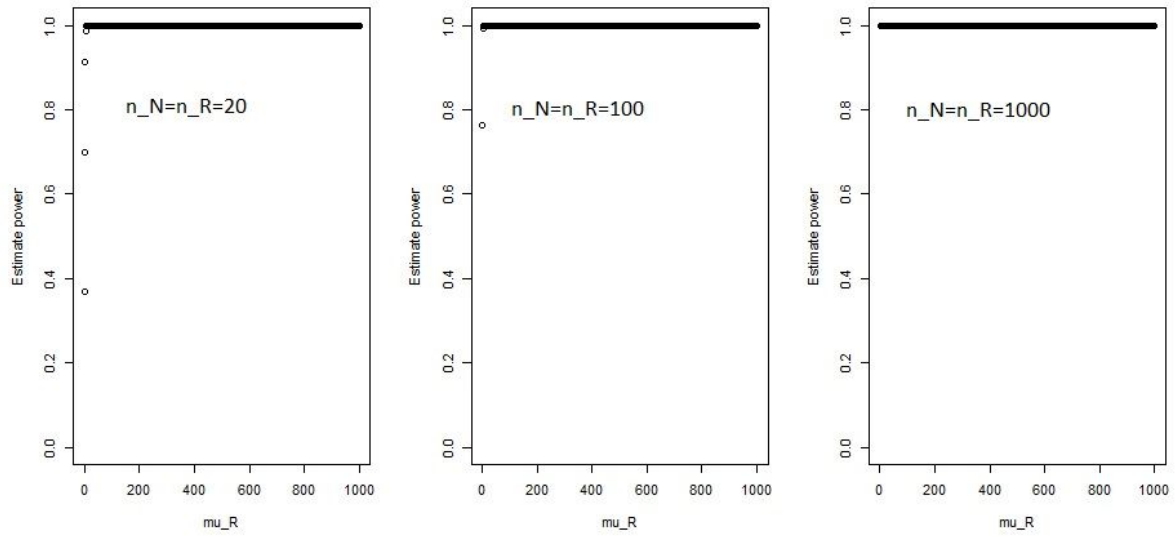


Figure 5

Type I error rate estimates according to sample sizes for the 95% two-sided confidence intervals level based test Type I error rate estimate as function of reference treatment, for the 95% two-sided confidence intervals level based test. From the left to the rigth, sample sizes are nN = nR = 20, 100 and 1000.



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Power estimates according to sample sizes for the 95% two-sided confidence intervals level based test
Power estimates as function of reference treatment, for the 95% two-sided confidence intervals level based test. From the left to the rigth, sample sizes are nN = nR = 20, 100 and 1000.