7. The Analysis of Equivalence and Non-Inferiority Trials

7.1 Equivalence Trials

Usually, the aim of a clinical trial is to test whether a new treatment is better than the existing standard treatment or a placebo. Such trials are sometimes called *Superiority Trials* as their purpose is to test whether one treatment is superior to another.

Some trials are designed to establish that two treatments are equally effective. A new drug may have fewer side-effects, be cheaper, or be more convenient than the current standard treatment. In such circumstances one may wish to establish that the new treatment has the same ability to treat the condition. For example some pain relief medications have side effects such as causing gastric bleeding or ulceration. A replacement therapy might have fewer side effects, but one may want to check that the two drugs have the same ability to relieve pain. Studies testing this type of hypothesis are called *Equivalence Trials*.

An equivalence trial design may be relevant to testing non-drug interventions. For example a trial to test whether say nurses were as effective as a general practitioner at delivering a particular type of care might wish to demonstrate that outcomes are the same.

Hypotheses for Equivalence Trials

In a *superiority* trial the hypotheses used for testing for a treatment effect are $H_0 : \tau = 0$ vs. $H_1 : \tau \neq 0$. It is sometime suggested that failure to reject $H_0 : \tau = 0$ mean that treatments are the same. This is incorrect as a small study that is underpowered would lead to this conclusion by default, whereas a larger trial might detect a small difference. The issue can be summed up by the statement "*An Absence of Evidence is not Evidence of Absence*". Use of a statistical test with the hypotheses above is therefore inappropriate for demonstrating equivalence.

This suggests the hypothesis for equivalence trials could be

$$H_0 : \tau \neq 0 \text{ vs. } H_1 : \tau = 0.$$

Unfortunately, it is never possible to show that two treatments are identical. Instead, one tests whether the treatment effect falls in range, say $(-\tau_E, \tau_E)$, called the *range of equivalence*. This should be defined by considering what range could be considered clinically equivalent. The hypotheses are now

$$H_0 : |\tau| \geq \tau_E \text{ vs. } H_1 : |\tau| < \tau_E$$

Rather than using formal significance testing, statistical analysis of equivalence trials is often based on the confidence interval of the difference between treatments. Equivalence is established by demonstrating that the confidence interval of the difference between treatment lies in the range of equivalence $(-\tau_E, \tau_E)$.

7.2 Analysis of Equivalence Trials for a Continuous Outcome Measures

Notation

Suppose n_T and n_C patients have been randomly allocated to groups *T* and *C* and suppose outcome measure *Y* is continuous and normally distributed with a mean μ_T for the new treatment and mean μ_C for the control so that the treatment effect $\tau = \mu_T - \mu_C$. Let $\bar{y}_T$ and $\bar{y}_C$ are the sample means and $\hat{\tau} = \bar{y}_T - \bar{y}_C$. As previously

$$SE[\hat{\tau}_C] = SE[\bar{y}_T - \bar{y}_C] = s\lambda$$

where $\lambda = \sqrt{1/n_T + 1/n_C}$ and the pooled sample standard deviation *s* is estimated by

$$s = \sqrt{\frac{(n_T - 1)s_T^2 + (n_C - 1)s_C^2}{n_T + n_C - 2}}$$

with s_T and s_C being the sample standard deviations for the two treatment groups. $t_\alpha(\nu)$ is the value of the t-distribution with $\nu = n_T + n_C - 2$ degrees of freedom having a cumulative probability equal $(1-\alpha)$.

Rejection of the null hypothesis that $H_0 : |\tau| \geq \tau_E$ vs. $H_1 : |\tau| < \tau_E$, when the $(1-2\alpha)$ confidence interval $(\hat{\tau} - t_\alpha(\nu)SE[\hat{\tau}], \hat{\tau} + t_\alpha(\nu)SE[\hat{\tau}])$ is within the interval $(-\tau_E, \tau_E)$, has a Type I error less than α.

Proof

To determine the Type 1 error we needs to estimate $\Pr[\text{Reject } H_0]$ under *H₀*. This probability depends on the value of τ. Since H_0 is a range of values of τ, $\Pr[\text{Reject } H_0]$ will take a range of values also.

$$\Pr[\text{Reject } H_0|\tau] = \Pr[(\hat{\tau} - t_\alpha(\nu)SE[\hat{\tau}], \hat{\tau} + t_\alpha(\nu)SE[\hat{\tau}]) \subseteq (-\tau_E, \tau_E)]$$

The distribution of $\hat{\tau}/SE[\hat{\tau}]$ has a non-central t-distribution, if $\tau \neq 0$.

To simplify the proof we will assume the variance is known, and equal to say σ, so $\hat{\tau}$ has a distribution $N[\tau, \sigma^2\lambda^2]$, so that we can replace $t_\alpha(\nu)$ with z_α. Hence

$$\begin{aligned}\Pr[\text{Reject } H_0|\tau] &\cong \Pr[(\hat{\tau} - z_\alpha\sigma\lambda, \hat{\tau} + z_\alpha\sigma\lambda) \subseteq (-\tau_E, \tau_E)] \\ &= \Pr[(\hat{\tau} - z_\alpha\sigma\lambda > -\tau_E) \cap (\hat{\tau} + z_\alpha\sigma\lambda < \tau_E)] \\ &= \Pr[(\hat{\tau} > -\tau_E + z_\alpha\sigma\lambda) \cap (\hat{\tau} < \tau_E - z_\alpha\sigma\lambda)]\end{aligned}$$

If $\tau_E \leq z_\alpha\sigma\lambda$, $(\hat{\tau} > -\tau_E + z_\alpha\sigma\lambda) \cap (\hat{\tau} < \tau_E - z_\alpha\sigma\lambda)$ is the null set, hence $\Pr[\text{Reject } H_0|\tau] = 0$.

If $\tau_E > z_\alpha\sigma\lambda$,

$$\begin{aligned}\Pr[\text{Reject } H_0|\tau] &= \Pr[\hat{\tau} < \tau_E - z_\alpha\sigma\lambda] - \Pr[\hat{\tau} < -\tau_E + z_\alpha\sigma\lambda] \\ &= \Phi\left(\frac{\tau_E - z_\alpha\sigma\lambda - \tau}{\sigma\lambda}\right) - \Phi\left(\frac{-\tau_E + z_\alpha\sigma\lambda - \tau}{\sigma\lambda}\right)\end{aligned}$$

See illustration below on page 97

The next step is to find τ that maximizes $\Pr[\text{Reject } H_0|\tau]$ under H_0.

Differentiation with respect to τ gives

$$\frac{d}{d\tau}\Pr[\text{Reject } H_0] = -\frac{1}{\sigma\lambda}\phi\left(\frac{\tau_E - \sigma\lambda z_\alpha - \tau}{\sigma\lambda}\right) + \frac{1}{\sigma\lambda}\phi\left(\frac{-\tau_E + \sigma\lambda z_\alpha - \tau}{\sigma\lambda}\right)$$

where ϕ is the density $N[0,1]$.

Since $\phi(z) = \phi(-z)$, it follows that

$$\phi\left(\frac{-\tau_E + \sigma\lambda z_\alpha - \tau}{\sigma\lambda}\right) = \phi\left(\frac{\tau_E - \sigma\lambda z_\alpha + \tau}{\sigma\lambda}\right).$$

Hence

$$\frac{d}{d\tau}\Pr[\text{Reject } H_0] = -\frac{1}{\sigma\lambda}\phi\left(\frac{\tau_E - \sigma\lambda z_\alpha - \tau}{\sigma\lambda}\right) + \frac{1}{\sigma\lambda}\phi\left(\frac{\tau_E - \sigma\lambda z_\alpha + \tau}{\sigma\lambda}\right),$$

which is zero when $\phi\left(\frac{\tau_E - \sigma\lambda z_\alpha - \tau}{\sigma\lambda}\right) = \phi\left(\frac{\tau_E - \sigma\lambda z_\alpha + \tau}{\sigma\lambda}\right)$.

Since $\tau_E > \sigma\lambda z_\alpha$, it follows that $\tau = 0$

Since $\Pr[\text{Reject } H_0]$ tend to zero as τ tends to $\pm\infty$, $\tau = 0$ must be maximum.

Hence $\Pr[\text{Reject } H_0]$ is monotone increasing for $\tau < 0$ and monotone decreasing for $\tau > 0$. Maximum of the Type 1 error are therefore the boundary values $\tau = -\tau_E$ and $\tau = \tau_E$.

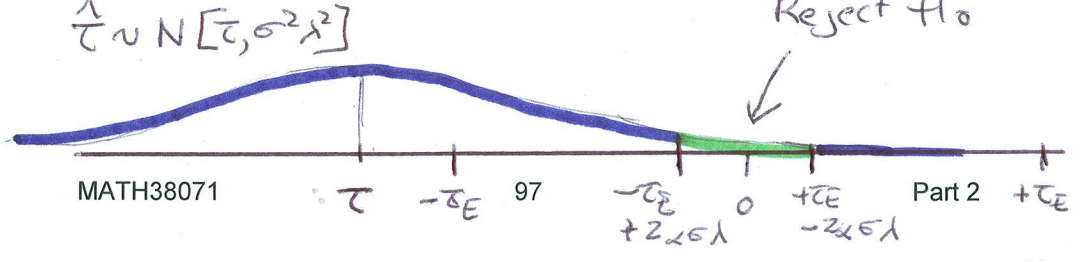
When $\tau = \tau_E$,

$$\Pr[\text{Reject } H_0] = \Phi\left(\frac{\tau_E - \sigma\lambda z_\alpha - \tau_E}{\sigma\lambda}\right) - \Phi\left(\frac{-\tau_E + \sigma\lambda z_\alpha - \tau_E}{\sigma\lambda}\right) \quad (*)$$

$$= \Phi(-z_\alpha) - \Phi(-2\tau_E/\sigma\lambda + z_\alpha) = \alpha - \Phi(z_\alpha - 2\tau_E/\sigma\lambda) < \alpha.$$

Similarly, when $\tau = -\tau_E$, $\Pr[\text{Reject } H_0] < \alpha$.

Therefore under the null hypothesis $H_0 : |\tau| \geq \tau_E$, $\Pr[\text{Reject } H_0] < \alpha$ as required ■



Ex 7.1. An equivalence trial is carried out to test the pain relief of a new medication thought to have fewer side effects than the current standard treatment. It was felt that mean pain score should not differ by more than 5 to demonstrate equivalent pain relief with higher pain scores representing greater pain. Fifty subjects were randomized to receive each treatment. Mean pain for the standard treatment is 45.1 (s.d.=20.6) and 46.3 (s.d.=19.4) for the new treatment. Test the null hypothesis of non-equivalence using a 5% significance level.

To achieve a 5% significance level one uses a 90% confidence interval. This is defined as

$$\bar{Y}_T - \bar{Y}_C \pm t_{0.05}(n_T + n_C - 2)\, SE\left[\bar{Y}_T - \bar{Y}_C\right]$$

$n_T = n_C = 50 \quad \bar{Y}_T = 46.3 \quad \bar{Y}_C = 45.1$

$s_T = 19.4 \quad s_C = 20.6$

$$s = \sqrt{\frac{49 \times 19.4^2 + 49 \times 20.6^2}{98}} = 20.01$$

$$SE\left[\bar{Y}_T - \bar{Y}_C\right] = 20.01 \times \sqrt{\frac{1}{50} + \frac{1}{50}} = \frac{20.01}{5}$$

90% C.I. is

$$1.2 \pm t_{0.05}(98) \times \frac{20.01}{5}$$

From Tables $t_{0.05}(95) = 1.66$ so use this

90% C.I. is -5.44 to 7.84

∴ We fail to reject the null hypothesis of non-equivalence as 90% C.I. is not within the range $(-5, 5)$

By default most computer packages give a 95% confidence intervals, but they can give confidence intervals with different levels of coverage if specified.

Figure 7.1 Stata output for a two sample t-test

2.5% significance level

(i) 95% confidence interval

```
Two-sample t test with equal variances
------------------------------------------------------------------------------
         |     Obs        Mean    Std. Err.   Std. Dev.   [95% Conf. Interval]
---------+--------------------------------------------------------------------
       x |      50        46.3     2.91328        20.6    40.44554    52.15446
       y |      50        45.1    2.743574        19.4    39.58658    50.61342
---------+--------------------------------------------------------------------
    diff |               1.2      4.0018               -6.741441    9.141441
------------------------------------------------------------------------------
    diff = mean(x) - mean(y)                                      t =   0.2999
Ho: diff = 0                                     degrees of freedom =       98

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.6175         Pr(|T| > |t|) = 0.7649          Pr(T > t) = 0.3825
```

(ii) 90% confidence interval

5% significance level

```
Two-sample t test with equal variances
------------------------------------------------------------------------------
         |     Obs        Mean    Std. Err.   Std. Dev.   [90% Conf. Interval]
---------+--------------------------------------------------------------------
       x |      50        46.3     2.91328        20.6    41.41574    51.18426
       y |      50        45.1    2.743574        19.4    40.50026    49.69974
---------+--------------------------------------------------------------------
    diff |               1.2      4.0018               -5.445193    7.845193
------------------------------------------------------------------------------
    diff = mean(x) - mean(y)                                      t =   0.2999
Ho: diff = 0                                     degrees of freedom =       98

    Ha: diff < 0                 Ha: diff != 0                 Ha: diff > 0
 Pr(T < t) = 0.6175         Pr(|T| > |t|) = 0.7649          Pr(T > t) = 0.3825
```

$\bar{Y}_T - \bar{Y}_C$ $SE\left[\bar{Y}_T - \bar{Y}_C\right]$

7.3 Sample Size for Equivalence Trials

Consider a continuous and normally distributed outcome measure Y with means μ_T and μ_C for the new and control treatment, and suppose the range of equivalence is $(-\tau_E, \tau_E)$. Assuming $\tau = 0$ under the alternative hypothesis $H_1 : |\tau| < \tau_E$, the sample size required to reject $H_0 : |\tau| \geq \tau_E$ using a $(1-2\alpha)$ confidence interval with power $(1-\beta)$ is $n = \frac{2\sigma^2}{\tau_E^2}(z_\alpha + z_{\beta/2})^2$ per treatment group assuming two equal size groups.

This formula assumes that sample size is sufficient such that the normal approximation for the t-distribution is valid.

The power is $\Pr[\text{Reject } H_0]$ under the alternative hypothesis H_1.

From the derivation above (*) on page 96

$$\Pr[\text{Reject } H_0] = \Phi\left(\frac{(\tau_E - \sigma\lambda z_\alpha) - \tau}{\sigma\lambda}\right) - \Phi\left(\frac{(-\tau_E + \sigma\lambda z_\alpha) - \tau}{\sigma\lambda}\right)$$

where $\lambda = \sqrt{\frac{1}{n_T} + \frac{1}{n_C}}$

Since $\tau = 0$ is assumed for the alternative hypothesis

$$Power = 1 - \beta = \Phi(\tau_E/\sigma\lambda - z_\alpha) - \Phi(-\tau_E/\sigma\lambda + z_\alpha)$$

Since $\Phi(x) = 1 - \Phi(-x)$, it follows that the second term

$$\Phi(-\tau_E/\sigma\lambda + z_\alpha) = 1 - \Phi(\tau_E/\sigma\lambda - z_\alpha).$$

Hence

$$1 - \beta = 2\Phi(\tau_E/\sigma\lambda - z_\alpha) - 1.$$

Rearrangement gives

$$1 - \beta/2 = \Phi(\tau_E/\sigma\lambda - z_\alpha).$$

Since $\Phi^{-1}(1-\beta/2) = z_{\beta/2}$, it follows that $z_{\beta/2} = \frac{\tau_E}{\sigma\lambda} - z_\alpha$.

Hence $\frac{\tau_E}{\sigma\lambda} = z_\alpha + z_{\beta/2}$

Assuming equal sample size $n_T = n_C = n$, then $\lambda = \sqrt{\frac{2}{n}}$.

Therefore $\sqrt{\frac{n}{2}} = \frac{\sigma}{\tau_E}(z_\alpha + z_{\beta/2})$.

Squaring and rearrangement gives $n = \frac{2\sigma^2}{\tau_E^2}(z_\alpha + z_{\beta/2})^2$ as required■

Ex 7.2 Pain relief trial continued. From the data above we have an estimate of $\sigma \cong 20$. Taking the range of equivalence as (-5,5) that is τ_E =5, estimate the minimum sample size per arm required to have 80% power to reject the null hypothesis of non-equivalence using a 90% confidence interval (i.e. 5% level test) assuming two equal size groups.

$$n = \frac{2\sigma^2}{\tau_E^2}(z_\alpha + z_{\beta/2})^2$$

From question use $\sigma = 20$ & $\tau_E = 5$

$\beta = 0.2 \Rightarrow z_{\beta/2} = z_{0.1} = 1.282$

$\alpha = 0.05 \Rightarrow z_\alpha = z_{0.05} = 1.645$

$$n = \frac{2 \times 20^2}{5^2}(1.645 + 1.282)^2 = 274.15$$

Minimum sample size to detect equivalence is 275 patients per group

7.4 Non-Inferiority Trials

In the trial comparing conservative treatment with suturing for small lacerations of the hand (Critical Appraisal 2), the objective was to establish that conservative management gave as good aesthetic outcome after 3 months. If conservative treatment gave a better outcome, one would not be concerned and would want to reject the null hypothesis as the main concern is check that conservative treatment did no worse.

If one is only concerned to demonstrate that a new treatment is as good or better, rather than equivalent to an existing treatment, only one bound is needed. This design is referred to as *non-inferiority* trials. Analysis of a non-inferiority trial can be based on a single-sided confidence interval. Note a (1-α) single-sided confidence interval is define by one or other limits of the usual two sided confidence interval, but with coverage (1-2α). So the upper and lower 95% single-sided confidence intervals are the upper and lower limits of a 90% confidence interval.

The hypotheses for a non-inferiority trial are therefore

$H_0 : \tau \le -\tau_N$ vs. $H_1 : \tau > -\tau_N$

if τ >0 represents benefit to the patient or

$H_0 : \tau \ge \tau_N$ vs. $H_1 : \tau < \tau_N$

if τ < 0 represents benefit.

Suppose Y is continuous and normally distributed outcome measure with a mean μ_T for the new treatment and mean μ_C for the control treatment so the treatment effect $\tau = \mu_T - \mu_C$. Suppose also that $\bar{y}_T$ and $\bar{y}_C$ are the sample means and $\hat{\tau} = \bar{y}_T - \bar{y}_C$.

(i) (Higher score for a better outcome) Rejection of the null hypothesis $H_0 : \tau \le -\tau_N$ vs. $H_1 : \tau > -\tau_N$ if the $(1-\alpha)$%single-sided confidence interval, given by $\hat{\tau} - t_\alpha(\nu) SE[\hat{\tau}]$, is greater than or equal to $-\tau_N$ will have a *Type 1* error ≤ α.

(ii) (Lower score for a better outcome) Rejection of the null hypothesis $H_0 : \tau \ge \tau_N$ vs. $H_1 : \tau < \tau_N$, if the $(1-\alpha)$% single-sided confidence interval, given by $\hat{\tau} + t_\alpha(\nu) SE[\hat{\tau}]$, is less than or equal to τ_N will have a *Type 1* error ≤ α.

(i) Higher score for a better outcome

Assuming a normal approximation to the t-distribution and a known standard deviation, σ, the $(1-\alpha)$% single sided lower confidence interval for $\hat{\tau}$ is given by $\hat{\tau} - z_\alpha \sigma\lambda$. H_0 will be rejected provided $\hat{\tau} - z_\alpha \sigma\lambda > -\tau_N$.

Therefore

$$\Pr[\text{Reject } H_0 | \tau] = \Pr[\hat{\tau} - z_\alpha \sigma\lambda > -\tau_N] = \Pr[\hat{\tau} > -\tau_N + \sigma\lambda z_\alpha].$$

Since $\hat{\tau}$ is $N[\tau, \sigma^2\lambda^2]$,

$$\Pr\left[\text{Reject } H_0 \middle| \tau\right] = 1 - \Phi\left(\frac{\left(-\tau_N + \sigma\lambda z_\alpha\right) - \tau}{\sigma\lambda}\right) = \Phi\left(\frac{\tau_N - \sigma\lambda z_\alpha + \tau}{\sigma\lambda}\right) \quad (**)$$

The maximum of this can be obtained by differentiation w.r.t. τ . The derivative is

$$\frac{d}{d\tau}\Pr\left[\text{Reject } H_0 \middle| \tau\right] = \frac{1}{\sigma\lambda}\phi\left(\frac{\tau_N - \sigma\lambda z_\alpha + \tau}{\sigma\lambda}\right) \quad (*)$$

where ϕ is the standard normal density function.

Since ϕ >0 for finite values, it follows that $\frac{d}{d\tau}\Pr\left[\text{Reject } H_0 \middle| \tau\right]$ is positive and so $\Pr\left[\text{Reject } H_0 \middle| \tau\right]$ is monotone increasing with τ.

Hence, the type 1 error rate has a maximum when $\tau = -\tau_N$.

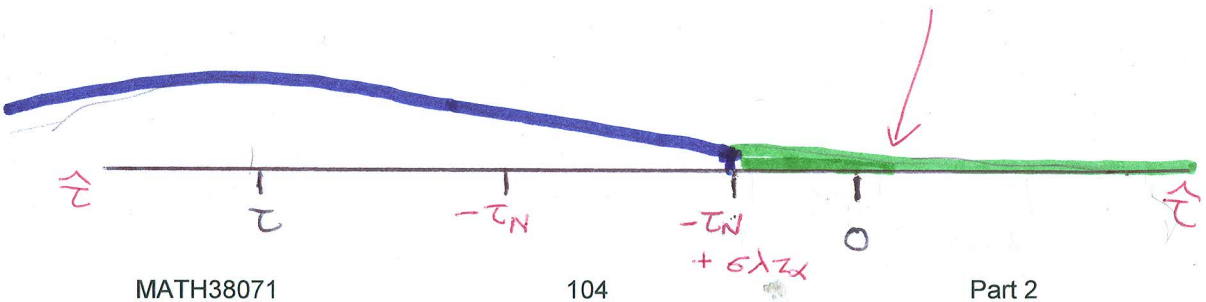
Setting $\tau = -\tau_N$, in (*)

$$\Pr\left[\text{Reject } H_0 \middle| \tau\right] = \Phi\left(\frac{\tau_N - \sigma\lambda z_\alpha - \tau_N}{\sigma\lambda}\right) = \Phi\left(-z_\alpha\right) = \alpha$$

Hence, the type 1 error must be less than or equal to α ■

Result (ii) is left as an exercise.

$\hat{\tau} \sim N[\tau, \sigma^2\lambda^2]$



Ex 7.3 Pain relief example continued. Assuming that higher pain scores represent more pain we would require the upper confidence interval to be less than 5. Are we able to show non-inferiority?

The hypothesis H_0 $\tau \geq 5$ is tested at a 5% significance level by the upper 95% c.i. (single sided) which is the upper limit of the two sided 90% C.I.

From above (E7.1) is 7.84.

Since this is above 5 one cannot reject H_0

7.5 Sample Size for Parallel Group Non-Inferiority Trials

Suppose higher scores represent a better outcome for the patient.

For a continuous and normally distributed with means μ_T and μ_C for the new treatment and control groups. If one considers treatment to be non-inferior provided the (1-α) % one-sided confidence interval for $\hat{\tau} = \bar{y}_T - \bar{y}_C$ is greater than $-\tau_N$, the sample size required to demonstrate non-inferiority with a power (1-β) is

$$n = \frac{2\sigma^2}{\tau_N^2}\left(z_\alpha + z_\beta\right)^2$$

per treatment group assuming $\tau = 0$ under the alternative hypothesis.

The derivation of the sample size formula for non-inferiority trials is similar to that for equivalence trials. Again the derivation will assume that sample size is sufficient for a normal approximation to the t-distribution is reasonable so that $\hat{\tau} \sim N\left[\tau, \sigma^2\lambda^2\right]$.

With higher score being a better outcome, one is testing $H_0 : \tau \le -\tau_N$ vs. $H_1 : \tau > -\tau_N$. From above (**) on page 104

$$\Pr\left[\text{Reject } H_0 \middle| \tau\right] = \Phi\left(\frac{\tau_N - \sigma\lambda z_\alpha + \tau}{\sigma\lambda}\right)$$

Under the alternative hypothesis, $\tau = 0$. Therefore, the power

$$1 - \beta = \Phi\left(\frac{\tau_N - z_\alpha\sigma\lambda}{\sigma\lambda}\right)$$

Since $\Phi^{-1}(1-\beta) = z_\beta$, by taking inverses $z_\beta = \frac{\tau_N}{\sigma\lambda} - z_\alpha$.

Hence $\frac{\tau_N}{\sigma\lambda} = z_\alpha + z_\beta$.

Assuming equal sample sizes $n_T = n_C = n$ then $\lambda = \sqrt{\frac{2}{n}}$.

Substitution gives the $\sqrt{\frac{n}{2}} = \frac{\sigma}{\tau_N}\left(z_\alpha + z_\beta\right)$ giving

$n = \frac{2\sigma^2}{\tau_N^2}\left(z_\alpha + z_\beta\right)^2$ as required ■

The derivation assuming lower scores are better is left as an exercise.

Ex 7.4 Pain relief trial continued. Calculate the sample size required to give 80% power to reject the null hypothesis of non-inferiority using a single-sided 95% confidence interval.

$n = \frac{2\sigma^2}{\tau_N^2}(z_\alpha + z_\beta)^2$

From page 101

$\sigma = 20$, $\tau_N = 5$ $z_\alpha = z_{0.05} = 1.645$

For 80% power

$z_\beta = z_{0.2} = 0.842$

$n = 2 \times \frac{20^2}{5^2}(1.645 + 0.842)^2 = 197.6$

Minimum sample size to demonstrate non-inferiority with 80% power is 198 per group, which is a slight reduction from that for equivalence (see page 101)

7.6 Limitations of Equivalence and Non-inferiority Trials

One problem with equivalence and non-inferiority trials is that poor design and sloppy implementation reduce the differences between treatment groups biasing the study towards the alternative hypothesis of equivalence. It is important therefore that patients adhere to their treatment in this type of trial. We will return to this point when we consider intention to treat analyses in the next section.

Equivalence trials show that two treatments may give the same average outcome but difference patients may benefit from a particular treatment. Equivalence trials do not demonstrate bio-equivalence, that is patients have the same outcome which ever treatment they receive.

Comparison of Sample Size Formulae for Parallel Group Trials and a Continuous Outcome

Sample size per group for a continuous outcome measure for difference hypotheses:

Superiority	$n = \frac{2\sigma^2}{\tau^2}\left(z_{\alpha/2} + z_{\beta}\right)^2$	– two sided
	$n = \frac{2\sigma^2}{\tau^2}\left(z_{\alpha} + z_{\beta}\right)^2$	– one sided
Equivalence	$n = \frac{2\sigma^2}{\tau_E^2}\left(z_{\alpha} + z_{\beta/2}\right)^2$	
Non-inferiority	$n = \frac{2\sigma^2}{\tau_N^2}\left(z_{\alpha} + z_{\beta}\right)^2$	

Note the similarities and differences between the formulae.