REVIEW ARTICLE

Superiority Trial: Sample Size Calculation and its Interpretation in Health Research

Ashok Kumar[1], Rimesh Pal[2], Manisha Nagi[3], Maninderdeep Kaur[4], Sukhpal Kaur[5]

Received on: 05 August 2022; *Accepted on:* 12 April 2023; *Published on:* 26 July 2023

Abstract

Sample size calculation in any randomized clinical trial is an essential step to avoid over- and underestimation of the outcomes. Health researchers should prior estimate the sample size which helps in the validity and reliability of the superiority trial. This paper highlights the step-by-step calculation of sample size in a superiority trial using appropriate and simple formulas and its interpretation with suitable examples in different conditions so that health researchers can better understand this important part of a clinical trial.

Keywords: Health research, Randomized clinical trial, Sample size calculation, Superiority trial.

Journal of Postgraduate Medicine, Education and Research (2023): 10.5005/jp-journals-10028-1623

What is Already Known?

- Sample size calculation in health research.
- Importance of sample size calculation in the clinical trial.
- Sample size calculation is considered a difficult part of the research.

What This Paper Adds?

- In-depth calculation with suitable examples along with simple explanations.
- Enhance confidence to calculate sample size in superiority trials in health research.
- Also, add the interpretation of sample size calculation results.

Introduction

In healthcare research, there are mainly three types of randomized controlled trials (RTCs); superiority trial, equivalence trial, and noninferior trial.[1] In a superiority trial, a researcher is interested to research out that new treatment (drug A) is superior to standard (old) treatment (drug B).[2] In this article, we will discuss sample size calculation in the superiority trial and its interpretation in detail which is a vital part of the trial.[3] Prior calculation of sample size is very important in any clinical trial or study to avoid over and underestimation of the study results.[4]

On the basis of the nature of the outcome of the study, there are mainly two conditions in which the superiority trial can be conducted.

Condition 1: When decrement (reduction) in dependent (outcome) variable is considered better (superior):

For quantitative outcome—decrement (reduction) in mean systolic blood pressure (SBP) in hypertensive patients or decrement (reduction) in mean anxiety score in patients.

For qualitative outcome—a decrement (reduction) in the proportion of bedsores in bedridden patients or a decrement (reduction) in the proportion of mortality in patients.

Condition 2: When increment (improvement) in dependent (outcome) variable is considered better (superior):

For quantitative outcome—increment (improvement) in quality of life (QOL) score in breast cancer patients.

For qualitative outcome: increment (improvement) in the success rate of any procedure or increment in satisfaction rate.

[1,3–5]Department of National Institute of Nursing Education, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

[2]Department of Endocrinology, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

Corresponding Author: Ashok Kumar, Department of National Institute of Nursing Education, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India, Phone: +91 9855012233, e-mails: ajangir_27@yahoo.in; ajangir5@gmail.com

How to cite this article: Kumar A, Pal R, Nagi M, *et al.* Superiority Trial: Sample Size Calculation and its Interpretation in Health Research. J Postgrad Med Edu Res 2023;57(3):131–136.

Source of support: Nil

Conflict of interest: Dr Sukhpal Kaur is associated as the National Editorial Board member of this journal and this manuscript was subjected to this journal's standard review procedures, with this peer review handled independently of this editorial board member and her research group.

Condition 1

Superiority Margin (θ_0)

Suppose we want to see a mean difference of –10 or a proportion difference of –10% (–0.10) between the new treatment group (drug A) and the old treatment group (drug B) at a certain time point.

Here, $\theta = -10$ or –10%

But on the contrary, we also want that this difference should not come equal to or greater than $= \theta_0 = -5$ (superiority margin), if this difference would come equal to or greater than –5, for example, suppose –4.5. So, this violates the condition of superiority trial and we have to conclude that drug A is not superior to drug B.

As we want to achieve the difference between the two treatments as –10; but not equal to or greater –5 ($\theta_0 = -5$) to fulfill the superiority trial condition. We have to judicially (logically) decide about the superiority margin in the superiority trial. Generally, it is taken as 0.

Hypothesis of Superiority Trial[5,6]

Condition 1A—when the dependent variable is quantitative in nature (mean) and decrement (reduction) in the dependent (outcome) variable is considered superior.

For example 1A—in an RTC, we want to see the effect of a new therapy in the reduction of mean SBP of patients by 10 mm Hg at 1-month follow-up compared to the control group taking the standard therapy.

Here;

μ_n = mean of SBP in new therapy group at 1-month follow-up = 130 mm Hg

μ_s = mean of SBP in standard (old) therapy group at 1-month follow-up = 140 mm Hg

θ = difference = $\mu_n - \mu_s$ = 130–140 = –10 mm Hg

θ_0 = superiority margin (as assumed by the researcher)= –5 mm Hg

H_0: null hypothesis = $\mu_n - \mu_s \geq \theta_0$ (here $\theta_0 = -5$)

H_1: alternate (research) hypothesis = $\mu_n - \mu_s < \theta_0$ (here $\theta_0 = -5$)

Formula for Sample Size Calculation for Superiority Trial[1,3,7–9]

$$n_1 \geq \frac{(r+1)(Z_{1-\alpha} + Z_{1-\beta})^2 \sigma^2}{r\left((\mu_n - \mu_s) - \theta_0\right)^2} \quad \text{(i)}$$

or

$$n_1 \geq \frac{(r+1)(Z_{1-\alpha} + Z_{1-\beta})^2 \sigma^2}{r(\theta - \theta_0)^2} \quad \text{(ii)}$$

Here,

r = ratio of sample size of group II (n_2 or standard (old) treatment group) and sample size of group I (n_1 or new treatment group) (usually r = 1; because $n_1 = n_2$; the number of subjects is same in each group).

Z = Standard Normal deviate function value (Table 1).

α = type I error rate; usually it is taken as 5% = 0.05.

β = type II error rate = 20% = 0.2; so, power of study = 1–β = 1–0.2 = 0.8 or 80%; if β = 0.10 then power of study will be 1–0.10 = 0.90 = 90%).

μ_n = mean of SBP in the new therapy group at 1-month follow-up = 130 mm Hg.

μ_s = mean of SBP in standard (old) therapy group at 1-month follow-up = 140 mm Hg.

θ_0 = superiority margin (as assumed by the researcher) = –5 mm Hg.

θ = difference = $\mu_n - \mu_s$ = 130–140 = –10 mm Hg.

σ = population/sample standard deviation (generally it is taken from the previous research studies or expert's assumptions and in this case, it is assumed as σ =10).

Now, using formula (i) or (ii) to calculate the sample size for the superiority trial:

$$n_1 \geq \frac{(r+1)(Z_{1-\alpha} + Z_{1-\beta})^2 \sigma^2}{r\left((\mu_n - \mu_s) - \theta_0\right)^2} \quad \text{(i)}$$

Put the values in the above formula and calculate the desired sample size:

$$n_1 \geq \frac{(1+1)*(1.645+0.842)^2*(10)^2}{1*\left((130-140)-(-5)\right)^2}$$

$$n_1 \geq \frac{(2)*(2.487)^2*(100)}{\left((-10)+5\right)^2}$$

$$n_1 \geq \frac{(2)*(6.19)*(100)}{(-5)^2}$$

$$n_1 \geq \frac{(12.38)*(100)}{25}$$

$$n_1 \geq \frac{1238}{25} = 49.52 = 50$$

How to Write Down "Sample Size Calculation Paragraph"

On the basis of the above calculation—"the researcher has to recruit 50 subjects in each group (N_T = total 100 subjects) in the study to achieve the reduction of mean SBP by at least 10 mm Hg at 1 month of follow-up in the new treatment group (drug A) as compared to standard treatment group (drug B) assuming standard deviation of 10 and superiority margin of –5 mm Hg at 80% power of the study and 95% confidence interval."

Adjustment for Dropout Rate/Attrition Rate

In follow-up/longitudinal studies, there may be chances of loss to follow-up or dropout of the study subjects. So, it is kept in mind before the study plan and sample size calculation and proper adjustment are done, and the final sample size calculation is done after adjustment of the anticipated dropout/attrition rate.

Formula for the Adjustment for Dropout Rate/Attrition Rate

$$N_A \geq \frac{N_T}{1-D}$$

Here,

N_A = sample size after adjustment of the dropout/attrition rate.

Table 1: Standard normal deviate function values[7,9,11]

α (type I error) or β (type II error) value	*Power of study = 1– β*	*α value at 95% confidence interval*	*Normal deviate function*	*Corresponding Z value*
0.2	1–0.2 = 0.8 = 80%		$Z_{1-\beta} = Z_{1-0.2}$	**0.842**
0.15				1.036
0.1	1–0.1= 0.9 = 90%		$Z_{1-\beta} = Z_{1-0.1}$	**1.282**
0.05		One-sided = α = 5% = 0.05	$Z_{1-\alpha}$	**1.645**
0.025		Two-sided = α/2 = 2.5% = 0.025	$Z_{1-\alpha/2}$	**1.960**
0.01				2.326
0.001				3.090

Note: Usually, the researchers take β = 0.2 for 80% power of study and β = 0.1 for 90% power of study and α = 0.05 for one-sided test, and α/2 = 0.05/2 = 0.025 for two-sided test. A one-sided test is used for superiority and noninferiority trials whereas a two-sided test is used for the equivalence trial; Researchers usually calculate sample size on bold parameters (corresponding Z value) in health research. So these values are given in bold (highlighted).

N_T = total sample size before adjustment.
D = dropout/attrition rate, that is, 10% = 0.10; 20% = 0.20
At a dropout rate of 10%, the final sample size would be:

$$\mathbf{N}_A \geq \frac{N_T}{1-D} = \frac{100}{1-0.10} = \frac{100}{0.9} = 111.11 = 112$$

So, with a 10% dropout rate, the researcher has to recruit a total of 112 subjects instead of 100.

And the sample size calculation paragraph would be like this—"the researcher has to recruit 50 subjects in each group (total 100 subjects) in the study to achieve the reduction of mean SBP by at least 10 mm Hg at 1 month of follow-up in the new treatment group (drug A) as compared to standard treatment group (drug B) assuming standard deviation of 10 and superiority margin of –5 mm Hg at 80% power of the study and 95% confidence interval. Anticipating a 10% dropout rate, a total of 112 subjects (56 subjects in each group) would be recruited in the current study."

Condition 1B—when the dependent variable is qualitative in nature (frequency/proportion) and decrement (reduction) in the dependent (outcome) variable is considered superior.

For example 1B—in an RTC, we want to see the effect of a new therapy in the reduction of the prevalence of bedsores among the patients by 25% (0.25) at 3 months follow-up compared to a control group who is taking standard therapy.

Here;

p_n = proportion of bedsore in new therapy group = 35% = 0.35
p_s = proportion of bedsores in standard (old) therapy group = 60% = 0.60
θ = difference = $p_n - p_s$ = 0.35–0.60 = –0.25
θ_0 = superiority margin (as assumed by the researcher) = –10% = –0.10
H_0: null hypothesis = $p_n - p_s \geq \theta_0$ (here θ_0 = –10%)
H_1: alternate (research) hypothesis = $p_n - p_s < -\theta_0$ (here θ_0 = –10%)
Formula for Sample Size Calculation for Superiority Trial[1,3,7–9]

$$n_1 \geq \frac{(Z_{1-\alpha} + Z_{1-\beta})^2 \left[p_n(1-p_n) + rp_s(1-p_s)\right]}{r\left((p_n - p_s) - \theta_0\right)^2}$$

or

$$n_1 \geq \frac{(Z_{1-\alpha} + Z_{1-\beta})^2 \left[p_n(1-p_n) + rp_s(1-p_s)\right]}{r(\theta - \theta_0)^2} \quad \text{(iv)}$$

Here,

$r = \frac{n2}{n1}$ = ratio of sample size of group II (*n*2 or standard (old) treatment group) and sample size of group I (*n*1 or new treatment group) (usually *r* = 1; because *n*1 = *n*2; the number of subjects is same in each group).
Z = standard normal deviation function value (see Table 1).
α = type I error rate = 5% = 0.05
β = type II error rate = 20% = 0.2; so, power of study = 1–β = 1–0.2 = 0.8 or 80%; if β = 0.10 then power of study will be 1–0.10 = 0.90 = 90%).
p_n = proportion of bedsore in new therapy group = 35% = 0.35
p_s = proportion of bedsores in standard (old) therapy group = 60% = 0.60
θ = difference = $p_n - p_s$ = 0.35–0.60 = –0.25
θ_0 = superiority margin (as assumed by the researcher) = –10% = –0.10

Now, using formula (iii) or (iv) to calculate the sample size for the superiority trial:

$$n_1 \geq \frac{(Z_{1-\alpha} + Z_{1-\beta})^2 \left[p_n(1-p_n) + rp_s(1-p_s)\right]}{r\left((p_n - p_s) - \theta_0\right)^2} \quad \text{(iii)}$$

Put the values in the above formula and calculate the desired sample size:

$$n_1 \geq \frac{(1.645 + 0.842)^2 \left[0.35(1-0.35) + 1*0.60(1-0.60)\right]}{1*\left((0.35 - 0.60) - (-0.10)\right)^2}$$

$$n_1 \geq \frac{(2.487)^2 \left[0.35(0.65) + 0.60(0.40)\right]}{\left((-0.25) + 0.10\right)^2}$$

$$n_1 \geq \frac{(6.19) * [0.23 + 0.24]}{(-0.15)^2}$$

$$n_1 \geq \frac{(6.19) * [0.47]}{0.023}$$

$$n_1 \geq \frac{2.91}{0.0225} = 129.33 = 130$$

How to Write Down "Sample Size Calculation Paragraph"
On the basis of the above calculation—the researcher has to recruit 130 subjects in each group (N_T = total 260 subjects) in the study to achieve the reduction of bedsore proportion/prevalence by at least 20% at 3 months of follow-up in the new treatment group (drug A) as compared to standard treatment group (drug B) assuming superiority margin of –10% at 80% power of the study and 95% confidence interval."

Formula for the Adjustment for Dropout Rate/Attrition Rate

$$N_A \geq \frac{N_T}{1-D}$$

Here,
N_A = sample size after adjustment of the dropout/attrition rate.
N_T = total sample size before adjustment.
D = dropout/attrition rate, that is, 10% = 0.10; 20% = 0.20
At a dropout rate of 10%, the final sample size would be:

$$N_A \geq \frac{N_T}{1-D} = \frac{100}{1-0.20} = \frac{260}{0.8} = 325$$

So, with a 20% dropout rate, the researcher has to recruit a total of 325 subjects instead of 260.

And the sample size calculation paragraph would be like this— "the researcher has to recruit 130 subjects in each group (total 260 subjects) in the study to achieve the reduction of bedsore prevalence/proportion by at least 20% at 3 months of follow-up in the new treatment group (drug A) as compared to standard treatment group (drug B) assuming superiority margin of –10% at 80% power of the study and 95% confidence interval. Anticipating a 20% dropout rate, a total of 326 subjects (163 subjects in each group) would be recruited in the current study."

Condition 2

Superiority Margin (θ_0)

Suppose we want to see a mean difference of 20 or a proportion difference of 20% between the new treatment group (drug A) and the old treatment group (drug B) at a certain time point.

Here, θ = 20

But on the contrary, we also want that this difference should not come equal to or below = θ_0 = 10 or 10% (superiority margin), if this difference would come equal to or below 10 for example suppose 9.25. So, this violet the condition of the superiority trial and we have to conclude that drug A is not superior to drug B.

As we want to achieve the difference between the two treatments as 20 or 20%; but not equal to or below 10 (θ_0 = 10 or 10%). It means this difference must be above at least 10 or 10% (θ_0) to fulfill the superiority trial condition. We have to judicially (logically) decide about the superiority margin in the superiority trial. Generally, it is taken as 0.

Hypothesis of Superiority Trial[5,6]

Condition 2A—when the dependent variable is quantitative in nature (mean) and increment or improvement in the dependent (outcome) variable is considered better (superior).

For example 2A—in an RTC, we want to see the effect of a new therapy in the improvement in the mean QOL score of the patients by 20 at 3 months follow-up compared to a control group who is taking standard therapy.

Here;

μ_n = mean of QOL score in new therapy group = 70

μ_s = mean of QOL score in standard (old) therapy group = 50

θ = difference = $\mu_n - \mu_s$ = 70–50 = 20

θ_0 = superiority margin (as assumed by the researcher) = 10

Hence, H_0: null hypothesis = $\mu_n - \mu_s \leq \theta_0$ (here, θ_0 = 10)

H_1: Alternate (research) Hypothesis: $\mu_n - \mu_s > \theta_0$

Formula for Sample Size Calculation[1,3,7–9]

$$n_1 \geq \frac{(r+1)(Z_{1-\alpha}+Z_{1-\beta})^2\sigma^2}{r\left((\mu_n-\mu_s)-\theta_0\right)^2} \quad \text{(i)}$$

or

$$n_1 \geq \frac{(r+1)(Z_{1-\alpha}+Z_{1-\beta})^2\sigma^2}{r(\theta-\theta_0)^2} \quad \text{(ii)}$$

Here,

$r = \frac{n2}{n1}$ = ratio of sample size of group II (n2 or standard (old) treatment group) and sample size of group I (n1 or new treatment group) (usually r = 1; because n1= n2; the number of subjects is same in each group.)

Z = standard normal deviation function value (see Table 1).

α = type I error rate = 5% =0.05

β = type II error rate = 20% = 0.2; so, power of study = 1–β = 1–0.2 = 0.8 or 80%; if β = 0.10 then power of study will be 1–0.10 = 0.90 = 90%).

μ_n = mean of QOL score in new therapy group = 70.

μ_s = mean of QOL score in standard (old) therapy group = 50

θ = difference = $\mu_n - \mu_s$ = 70–50 = 20

θ_0 = superiority margin (as assumed by the researcher) = 10

σ = population/sample standard deviation (generally it is taken from the previous research studies or expert assumptions and in this case, it is assumed as σ =15).

Now, using formula (i) or (ii) to calculate the sample size for superiority trial:

$$n_1 \geq \frac{(r+1)(Z_{1-\alpha}+Z_{1-\beta})^2\sigma^2}{r\left((\mu_n-\mu_s)-\theta_0\right)^2}$$

Put the values in the above formula and calculate the desired sample size:

$$n_1 \geq \frac{(1+1)*(1.645+0.842)^2*(15)^2}{1*\left((70-50)-10\right)^2}$$

$$n_1 \geq \frac{(2)*(2.487)^2*(225)}{\left((20)-10\right)^2}$$

$$n_1 \geq \frac{(2)*(6.19)*(225)}{(10)^2}$$

$$n_1 \geq \frac{(12.38)*(225)}{100}$$

$$n_1 \geq \frac{2785.5}{100} = 27.855 = 28$$

Condition 2B—when the dependent variable is qualitative in nature (frequency/proportion) and increment or improvement in the dependent (outcome) variable is considered better (superior).

For example—in an RTC, we want to see the effect of a new therapy in increment in success rate among the patients by 20% (0.20) at 3 months follow-up compared to a control group who is taking standard therapy.

Here;

$\mu_n = p_n$ = proportion of success in new therapy group = 45% = 0.45

$\mu_s = p_s$ = proportion of success in standard (old) therapy group = 25% = 0.25

θ = actual difference = $p_n - p_s$ = 0.45–0.25 = 0.20

θ_0 = superiority margin (as assumed by the researcher) = 0.10

H_0: null hypothesis = p_n—$p_s \leq \theta_0$ (here, θ_0 = 10)

H_1: Alternate (research) hypothesis—$p_n - p_s > \theta_0$

Formula to Calculate Sample Size[1,3,7–9]

$$n_1 \geq \frac{(Z_{1-\alpha}+Z_{1-\beta})^2\left[p_n(1-p_n)+rp_s(1-p_s)\right]}{r\left((p_n-p_s)-\theta_0\right)^2} \quad \text{(iii)}$$

or

$$n_1 \geq \frac{(Z_{1-\alpha}+Z_{1-\beta})^2\left[p_n(1-p_n)+rp_s(1-p_s)\right]}{r(\theta-\theta_0)^2} \quad \text{(iv)}$$

Here,

$r = \frac{n2}{n1}$ = ratio of sample size of group II (n2 or standard (old) treatment group) and sample size of group I (n1 or new treatment group) (usually r = 1; because n1= n2; the number of subjects are same in each group.)

Z = standard normal deviation function value (see Table 1).

α = type I error rate = 5% =0.05

β = type II error rate = 20% = 0.2; so, power of study = 1–β = 1–0.2 = 0.8 or 80%; if β = 0.10 then power of study will be 1–0.10 = 0.90 = 90%).

p_n = proportion of success in new therapy group = 45% = 0.45

p_s = proportion of success in standard (old) therapy group = 25% = 0.25

θ = difference = $p_n - p_s$ = 0.45–0.25 = 0.20

θ_0 = superiority margin (as assumed by the researcher) = 0.10

Now, using formula iii (or iv) to calculate sample size for the superiority trial:

$$n_1 \geq \frac{(Z_{1-\alpha}+Z_{1-\beta})^2\left[p_n(1-p_n)+rp_s(1-p_s)\right]}{r\left((p_n-p_s)-\theta_0\right)^2} \quad \text{(iii)}$$

Put the values in the above formula and calculate the desired sample size:

$$n_1 \geq \frac{(1.645+0.842)^2\left[0.45(1-0.45)+1*0.25(1-0.25)\right]}{1*\left((0.45-0.25)-0.10\right)^2}$$

$$n_1 \geq \frac{(2.487)^2\left[0.45(0.55)+0.25(0.75)\right]}{\left((0.20)-0.10\right)^2}$$

$$n_1 \geq \frac{(6.19)*\left[0.248+0.188\right]}{(0.10)^2}$$

$$n_1 \geq \frac{(6.19)*\left[0.436\right]}{0.0100}$$

$$n_1 \geq \frac{2.6988}{0.0100} = 269.88 = 270$$

Examples

Condition 1A—when the dependent variable is quantitative in nature (mean) and decrement (reduction) in the dependent (outcome) variable is considered superior.

Example 1 A—in a superior RTC, the researcher wants to assess the effect of a new exercise program on the mean cholesterol level of patients at 6 weeks compared to the control group. All the parameters are as follows:

μ_n = mean cholesterol level of patients in a new exercise program at 6 weeks = 150 mg/dL

μ_s = mean cholesterol level of patients in a standard (old) therapy group at 6 weeks = 220 mg/dL

θ = difference = $\mu_n - \mu_s$ = 150–220 = –70 mg/dL

θ_0 = superiority margin (as assumed by the researcher)= –25 mg/dL

σ = population/sample standard deviation (generally it is taken from the previous research studies or expert's assumptions and in this case, it is assumed as σ = 80) (Table 2).

Formula for Sample Size Calculation for Superiority Trial

$$n_1 \geq \frac{2*(Z_{1-\alpha}+Z_{1-\beta})^2\sigma^2}{(\theta-\theta_0)^2}$$ (note: $Z_{1-\alpha}$ = 1.645 at 5% level of significance; $Z_{1-\beta}$ = 0.842 at 80% power of study.)

Table 2: Requirement for sample size calculation in superiority trial[3,9]

Requirement	*Details*
Type I error (α)	0.05 {At 95% confidence interval (one-sided)}
Type II error (β) Power of study = 1–β	At β = 0.1 so, power of study = 1–β = 1–0.1 = 0.9 = 90% At β = 0.2 so, power of study = 1–β = 1–0.2 = 0.8 = 80%
Primary outcome/ endpoint	Quantitative (mean difference) or qualitative/ categorical (proportion/percentage difference)
Difference of primary outcome/ endpoint between two groups	$\theta = \mu_n - \mu_s$ [for quantitative outcome/endpoint (mean difference)] $\theta = \rho_n - \rho_s$ [for qualitative/categorical outcome/ endpoint (proportion/percentage difference)]
Superiority margin	θ_0 = Superiority margin (as assumed by the researcher)
Population/sample standard deviation	σ/s (generally it is taken from previous research studies or expert assumptions)

0.05, Researchers usually calculate sample size on Type I error at 0.05 and corresponding Z value (bold numbers) in health research. So these values are given in bold (highlighted).

Put the values in the above formula and calculate the desired sample size:

$$n_1 \geq \frac{2*(1.645+0.842)^2*(80)^2}{\left(-70(-25)\right)^2}$$

$$n_1 \geq \frac{(2)*(2.487)^2*(6400)}{(-70+25)^2}$$

$$n_1 \geq \frac{(2)*(6.19)*(6400)}{(-50)^2}$$

$$n_1 \geq \frac{(12.38)*(6400)}{2500}$$

$$n_1 \geq \frac{79232}{2500} = 31.69 = 32$$

So, the researcher has to enroll at least 32 patients in each group (a total of 64) for this trial.

Condition 1B—when the dependent variable is qualitative/ dichotomous in nature (frequency/proportion) and decrement (reduction) in the dependent (outcome) variable is considered superior.

Example 1B—in a superiority RTC, the researcher wants to assess the effect of mobile app strategy on the reduction of composite poststroke complications among bedridden stroke survivors compared to standard care at 3 months follow-up. All the parameters are as follows:

p_n = proportion of composite poststroke complications in mobile app group = 33.8% = 0.338.

p_s= proportion of composite poststroke complications in standard (old) therapy group = 56.4% = 0.564.

θ = difference = $p_n - p_s$= 0.338–0.564 = –0.226

θ_0 = superiority margin (as assumed by the researcher) = –5% = –0.05

Formula for Sample Size Calculation for Superiority Trial

$$n_1 \geq \frac{(Z_{1-\alpha}+Z_{1-\beta})^2\left[p_n(1-p_n)+p_s(1-p_s)\right]}{(\theta-\theta_0)^2}$$ (note: $Z_{1-\alpha}$ = 1.645 at 5% level of significance; $Z_{1-\beta}$ = 0.842 at 80% power of study.)

Put the values in the above formula and calculate the desired sample size:

$$n_1 \geq \frac{(1.645+0.842)^2\left[0.338(1-0.338)+0.564(1-0.564)\right]}{\left((-0.226)-(-0.05)\right)^2}$$

$$n_1 \geq \frac{(2.487)^2\left[0.338(0.662)+0.564(0.436)\right]}{\left((-0.226)+0.05\right)^2}$$

$$n_1 \geq \frac{(6.19)*[0.22+0.25]}{(-0.18)^2}$$

$$n_1 \geq \frac{(6.19)*[0.47]}{0.032}$$

$$n_1 \geq \frac{2.91}{0.032} = 90.9 = 91$$

So, the researcher has to enroll at least 91 patients in each group (a total of 182) for this trial.

Condition 2A—when the dependent variable is quantitative in nature (mean) and increment or improvement in the dependent (outcome) variable is considered better (superior).

Example 2A—in a superiority RTC, the researcher wants to assess the effect of a new diet regimen in the improvement in the mean hemoglobin (Hb) among anemic patients at 1-month follow-up compared to the control group. All the parameters are as follows:

μ_n = mean Hb in the new diet regimen group at 1 month = 14.0 mg/dL.

μ_s = mean Hb in control group = 10 mg/dL.

θ = difference = $\mu_n - \mu_s$ = 14–10 = 4 mg/dL.

θ_0 = superiority margin (as assumed by the researcher) = 2.

σ = population/sample standard deviation (generally it is taken from the previous research studies or expert assumptions and in this case, it is assumed as σ =3).

Formula for Sample Size Calculation for Superiority Trial

$$n_1 \geq \frac{2*(Z_{1-\alpha}+Z_{1-\beta})^2\sigma^2}{(\theta-\theta_0)^2}$$ (note: $Z_{1-\alpha}$ = 1.645 at 5% level of significance; $Z_{1-\beta}$ = 0.842 at 80% power of study.)

Put the values in the above formula and calculate the desired sample size:

$$n_1 \geq \frac{2*(1.645+0.842)^2*(3)^2}{(4-2)^2}$$

$$n_1 \geq \frac{(2)*(2.487)^2*(9)}{(4-2)^2}$$

$$n_1 \geq \frac{(2)*(6.19)*(9)}{(2)^2}$$

$$n_1 \geq \frac{(12.38)*(9)}{4}$$

$$n_1 \geq \frac{111.42}{4} = 27.855 = 28$$

So, the researcher has to enroll at least 28 patients in each group (a total of 56) for this trial.

Condition 2B—when the dependent variable is qualitative/dichotomous in nature (frequency/proportion) and increment or improvement in the dependent (outcome) variable is considered better (superior).

Example 2B—In a superior RTC, the researcher wants to assess the effect of a new therapy on the satisfaction rate among the breast cancer survivors at 3 months follow-up compared to the control group.

$\mu_n = p_n$ = proportion of satisfaction in new therapy group = 80% = 0.80.

$\mu_s = p_s$ = proportion of satisfaction in control group = 50% = 0.50.

θ = actual difference = $p_n - p_s$ = 0.80–0.50 = 0.30.

θ_0 = superiority margin (as assumed by the researcher) = 15% = 0.15.

Formula for Sample Size Calculation for Superiority Trial

$$n_1 \geq \frac{(Z_{1-\alpha}+Z_{1-\beta})^2\left[p_n(1-p_n)+p_s(1-p_s)\right]}{(\theta-\theta_0)^2}$$ (note: $Z_{1-\alpha}$ = 1.645 at 5% level of significance; $Z_{1-\beta}$ = 0.842 at 80% power of study.)

Put the values in the above formula and calculate the desired sample size:

$$n_1 \geq \frac{(1.645+0.842)^2\left[0.80(1-0.80)+1*0.50(1-0.50)\right]}{1*(30-0.15)^2}$$

$$n_1 \geq \frac{(2.487)^2\left[0.80(0.20)+0.50(0.50)\right]}{(0.30-0.15)^2}$$

$$n_1 \geq \frac{(6.19)*[0.16+0.25]}{(0.15)^2}$$

$$n_1 \geq \frac{(6.19)*[0.41]}{0.0225}$$

$$n_1 \geq \frac{2.538}{0.0225} = 112.79 = 113$$

So, the researcher has to enroll at least 113 patients in each group (a total of 226) for this clinical superiority trial.

(note: dropout/nonresponse rate adjustment—we have to adjust sample size for dropout rate or nonresponse rate).

Conclusion

Sample size calculation in clinical superiority trials is essential. Health researchers should be acquainted with calculated sample sizes in clinical trials. This article provides thorough and step-by-step calculation and interpretation of sample size calculation in superiority trials in health research.

Orcid

Ashok Kumar https://orcid.org/0000-0002-1691-4953
Rimesh Pal https://orcid.org/0000-0003-4859-9393
Manisha Nagi https://orcid.org/0000-0001-8284-5979
Maninderdeep Kaur https://orcid.org/0000-0003-3446-8851
Sukhpal Kaur https://orcid.org/0000-0003-3724-1310

References

1. Wang B, Wang H, Tu Xm, et al. Comparisons of superiority, non-inferiority, and equivalence trials. Shanghai Arch Psychiatry 2021;29(6):385–388. DOI: 10.11919/j.issn.1002-0829.217163
2. Kishore K, Mahajan R. Understanding superiority, noninferiority, and equivalence for clinical trials. Indian Dermatol Online J 2020;11(6):890–894. DOI: 10.4103/idoj.IDOJ_130_20
3. Flight L, Julious SA. Practical guide to sample size calculations: superiority trials. Pharm Stat 2016;15(1):75–79. DOI: 10.1002/pst.1718
4. Sakpal TV. Sample size estimation in clinical trial. Perspect Clin Res 2010;1(2):67–69. PMC3148614 PMC3148614
5. Chow S-C, Shao J, Wang H, editors. Sample size calculations in clinical research: New York: Marcel Dekker; 2003. 358p. (Biostatistics).
6. Chow S-C, Shao J, Wang H, et al. Sample Size Calculations in Clinical Research: Third Edition [Internet]. 3rd ed. Chow S-C, Shao J, Wang H, Lokhnygina Y, editors. Third edition. | Boca Raton : Taylor & Francis, 2017. | Series: Chapman & Hall/CRC biostatistics series | "A CRC title, part of the Taylor & Francis imprint, a member of the Taylor & Francis Group, the academic division of T&F Informa plc.": Chapman and Hall/CRC; 2017 [cited 2021 May 11]. Available from: https://www.taylorfrancis.com/books/9781351727129
7. Flight L, Julious SA. Practical guide to sample size calculations: non-inferiority and equivalence trials. Pharm Stat 2016;15(1):80–89. DOI: 10.1002/pst.1716
8. Hwang IK, Morikawa T. Design Issues in noninferiority/equivalence trials. Drug Inf J 1999;33(4):1205–1218. DOI: 10.1177/009286159903300424
9. Zhong B. How to calculate sample size in randomized controlled trial? J Thorac Dis 2009;1(1):51–54. PMC3256489