# Therapeutic efficacy evaluation studies

## The purpose and usefulness of this practical activity

• Understanding and applying the methodological aspects of the therapeutic efficiency evaluation and quantification studies

• Understanding and applying the methods for analyzing, reporting and interpreting the results of a therapeutic efficacy assessment and quantification study

## Scenario

A randomized, placebo-controlled, double-blind, trial with parallel groups was conducted to verify the therapeutic efficacy of the 300 mg / day dose of aspirin, administered orally for 24 weeks, in favoring healing of lower limb venous (varicose) ulcers, in the presence of background therapy using mechanical compression administered to all studied patients.

Adult patients from 7 regional healthcare and recovery centers from Romania were selected for the study with the following inclusion criteria: patients who could tolerate compression of lower limb with elastic stockings, able to give informed consent for study participation, whose family doctor confirmed that they could be treated safely with aspirin 300 mg / day, and who had a confirmed diagnosis of venous ulcer of the lower limb.

Exclusion criteria were: breastfeeding mothers, those with a history of myocardial infarction, stroke, transient ischemic attack, angina pectoris, major peripheral arterial disease, patients with a history of side effects related to the use of aspirin (hypersensitivity, allergy, aspirin-induced asthma), patients already taking aspirin or other anticoagulant therapy; patients with coexisting conditions or treatments indicating or, on the contrary, contraindicating the use of aspirin, as well as patients considered for any other reason to be unable to participate in this clinical trial or who have not given informed consent to participate in the study.

After the recruitment phase, 400 patients with lower limb varicose ulcers were included into the study, having different evolution stages of the ulceration(s). Two hundred of these patients were randomized to the experimental group (aspirin + mechanical compression) and 200 in the control group (placebo + mechanical compression).

The adjuvant treatment (aspirin or placebo) was self-administered by patients without the patients or health professionals that measured the response to the treatment knowing to which group (aspirin vs. placebo) each patient belonged.

Randomization was centralized. The person who introduced the subjects into the study, phoned the randomization center, provided patient data and received the treatment code that was then given to the patient. The significance of the code was known only to the hospital pharmacy.

Healing of the varicose ulcer was defined as the complete re-epithelialization of the baseline ulceration (the highest initial diameter ulcer in each patient) after 24 weeks of mechanical compression + adjuvant treatment.

The frequency of healing in the experimental group (treated with aspirin 300 mg / day) and that in the control group (placebo treated) was compared.

The difference between the experimental and the control group in terms of reduction in the reference ulcer diameter after the 24 weeks of treatment was also analyzed.

For both comparisons, the patients were analyzed in the groups in which they were originally randomized, and the measurements and analyzes were performed by researchers who did not know which group the evaluated subjects belonged to.

The experimental data of this study are available in the BD\_RCTen.xls file.

**Clinical question:** Is the aspirin dose of 300 mg / day for 24 weeks more effective than placebo in healing varicose ulcers of the inferior limbs, when administered orally, as an adjuvant therapy associated to a background therapy of mechanical compression of the lower limb?

## Research Protocol

1. Write the aim and objectives of this study:

**Aim:**

**Objective:**

1. Write the research domain of this study:

### Research domain:

1. Write the type of this study according to the:

|  |
| --- |
| A. Based on study objectives (fill in): |
| B. Based on the results (fill in): |
| C. Depending on the trial design (fill in): |
| D. Depending on the objective (fill in): |
| E. Depending on the hypothesis (fill in): |
| F. Depending on the drug development phase (fill in): |

**The methods used to ensure the validity of the study**

* Did the subjects have been assigned to random treatments? (YES / Unclear / NO)
* Was it stated if the allocation was concealed ("allocation concealed")? (YES / Unclear / NO)
* Have all patients been analyzed in the appropriate group for what they were given? (analysis was of the "safety analysis set" type?) ")? (YES / Unclear / NO)
* Was the double blind method used? (YES / Unclear / NO)
* Was the trial controlled? (YES / Unclear / NO)

1. What was the target population of this study?

#### **Target population:**

1. What was the accessible population of this study?

#### **Accessible population:**

1. Describe the study sample:

##### **Study sample:**

##### Inclusion criteria:

Demographics:

Clinical features:

#### Exclusion criteria (applied to subjects meeting the inclusion criteria; some may be missing):

#### Biasing factors (e.g. coexistent diseases/coexistent treatments):

#### Side effects:

#### Factors that make data collection difficult or impossible:

#### Ethical issues:

#### 

1. **Sample size**

#### Is the size of the studied sample sufficient? Answer this question knowing that at the bibliographic study stage of the study, a 75% frequency of varicose ulcer healing was estimated to appear by mechanical compression treatment only, and the study aimed to prove an improvement by at least 15% of this healing rate in the presence of aspirin 300 mg / day adjuvant treatment, with a statistical power of at least 90%. Using the STATCALC option of Epiinfo, the minimum sample size required to meet the above conditions was estimated to be 292 participants (146 subjects in each of the two groups that have been randomized in a 1: 1 ratio).

#### The proportion of subjects lost from the study was estimated to be at most 25%.

#### Open the **BD\_RCTen.xls** database and assess wether the sample size was large enough or not! When assessing if the sample size was sufficient, you should add 25% to the estimated sample volume (146\*2)!

#### **Is the size of the studied sample large enough? (Yes/No):**

1. Write the data collection method:

**Based on the studied population:**

**Based on the duration of data collection:**

**Based on the grouping method:**

1. Write the name of the variables from the BD\_RCTen.xls file into the correct boxes below (D1Ulceration (mm) = Initial diameter of the ulceration (mm); D2Ulceration (mm) = Final diameter of the ulceration (mm); D1-D2 (mm) = Reduction of the ulcer diameter (mm)):

|  |  |  |
| --- | --- | --- |
| 1. **Qualitative variables** | | |
| Nominal | Nominal dichotomous | Ordinal |
| 1. **Quantitative** | | |
| Continuous | Discrete | |

1. Write the method(s) that you will use **for the description** of the above variables:

|  |
| --- |
| **Qualitative variables** (described by frequency tables or pie charts, column / bars, etc.) |
|  |
| **Quantitative variables** (described by: i) point indicators in the format: *mean ± standard deviation* or *median and interquartile range*: median [1st quartile; 3rd quartile]; or ii) *histogram* - for describing the distribution or iii) *error plot* for normally distributed variables, or iv) *box and whiskers* chart *(box plot)* for quantitative variables that do not follow a normal distribution).  The variables ***D1Ulceration (mm)*** and ***D1-D2 (mm)*** are normally distributed (p>0.05) and ***D2Ulceration (mm)*** does not follow normal distribution (p<0.01). |
|  |

1. Write the statistical method that you will use **for describing the association** between the type of treatment (*Aspirin*) and the healing of the varicose ulcer of the inferior limb (*Healing*):

|  |
| --- |
| **Qualitative variables** (described by contingency table or column / bar graph) |
|  |

1. Write the inferential statistic method that you will use **for testing the association between** the treatment type and the healing of the lower limb varicose ulcer:

|  |
| --- |
| **Qualitative variables** (independent groups: Hi-square test if at least 80% of theoretical frequencies will be > 5, otherwise: Fisher's exact test; dependent groups: McNemar test) |
|  |

1. Write the inferential statistic method that you will use for testing the association between the treatment type and the diameter reduction of the reference ulcer:

|  |
| --- |
| **Normally distributed quantitative variables** (independent groups: t-Student test for independent samples, dependent groups: t-Student test for paired samples)  **Quantitative variables in the absence of normal distribution** (independent groups: Test U, Mann-Whitney, dependent groups: Wilcoxon Test for Pairs) |
|  |

1. Write the generic formulas (using the **a, b, c, d frequencies** of a generic contingency table) of the point estimates of the medical indicators that measures the therapeutic effect of aspirin 300 mg/day in the treatment of varicose ulcer in the studied sample:

|  |
| --- |
| **ARR=|REE-REC|=**  **NNT=**  **RR=**  In the results section, the above point estimates will be calculated and presented along with their confidence interval, for example ARR (95%CI lower limit-upper limit) |

## Results. Data analysis and presentation of results

### Studying the comparability of the groups that have resulted after the randomization of the studied sample:

### A. Verify whether the initial (baseline) diameter of the reference ulceration was significantly different in the experimental group compared to the placebo group (Jamovi, Analyses, T-Tests, Independent samples T-Test, Grouping variable : Aspirin, Dependent variable : D1 Ulceration (mm). Options : Student, Welch, Mean difference, Confidence interval, Descriptives, Descriptives plots, Homogeneity tests, Normality test, Q-Q plot).

**B.** Verify whether the sex of the patients was equally distributed in the experimental group versus the placebo group **(Jamovi, Analyses, Independent Samples (x2 test of association)**, **Rows: Aspirin**, **Columns: Sex**, Optionsi: Tests: **X2**, **Fisher’s exact test**; Comparative measures (2x2 only) (Change by data collection type by grouping): **Relative risk**, attributable risk/absolute risk reduction (**Difference in proportion**), **Confidence intervals**; Counts: **Observed counts**, **Expected counts**; Percentages: **Row**; Plots: **Bar Plot**, **Y-Axis**: **Percentages**, **within rows**; **Bar Type** Stacked; **X-Axis**: **Rows**.

Requirements A and B are exemplified in Table 1.

**Table 1. Initial characteristics of the randomized groups**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **Aspirin (n=200)** | **Placebo (n=200)** | **p** |
| D1Ulceration(mm) - mean (standard deviation) | 24.03 (3,83) | 23.43 (3.98) | 0.124 |
| Women - no. (%) | 106 (53.0) | 113 (56.5) | 0.482 |

**Evaluation of the existence of a therapeutic effect:**

**C.** Verify whether the ulcer diameter reduction was significantly different in the experimental group compared to the placebo group(**Jamovi, Analyses, T-Tests, Independent samples T-Test, Grouping variable : Aspirin, Dependent variable : D1-D2 (mm).** Options : Student, Welch, Mean difference, Confidence interval, Descriptives, Descriptives plots, Homogeneity tests, Normality test, Q-Q plot)**.** Complete the results in Table 2.

**D.** Verify whether a statistically significant relationship between the type of treatment and the healing of varicose ulcer exists **(Jamovi, Analyses, Independent Samples (x2 test of association)**, **Rows: Aspirin**, **Columns: Recovery**, Options: Tests: **X2**, **Fisher’s exact test**; Comparative measures (2x2 only) (Change by data collection type by grouping): **Relative risk**, attributable risk/absolute risk reduction (**Difference in proportion**), **Confidence intervals**; Counts: **Observed counts**, **Expected counts**; Percentages: **Row**; Plots: **Bar Plot**, **Y-Axis**: **Percentages**, **within rows**; **Bar Type** Stacked; **X-Axis**: **Rows**. Complete the results in Table 2:

**Table 2. Average reduction of ulcer diameters (mm) and the frequency of varicose ulcer recovery (healing) in the experimental group compared to the control group**

|  |  |  |  |
| --- | --- | --- | --- |
| **Characteristic** | **Aspirin (n=200)** | **Placebo (n=200)** | **p** |
| D1-D2(mm) - mean (standard deviation) |  |  |  |
| Recovery - no. (%) |  |  |  |

Values are presented as mean (standard deviation) for data following a normal distribution, median (1st quartile – 3rd quartile) for data not following a normal distribution; number of subjects (percent), n - number of subjects.

**E**. **Contingency table** between the type of treatment and varicose ulcer healing (see above):

**Table 3. Distribution of ulcer healing (Recovery) by treatment type**

|  |  |  |  |
| --- | --- | --- | --- |
| **Observed frequencies** | Recovery = Yes | Recovery = No | Total |
| Aspirin = yes |  |  |  |
| Aspirin = no |  |  |  |
| Total |  |  |  |

**F. Indicators that measure the effect of the evaluated drug compared to the reference treatment:** Based on the contingency table above, calculate the medical indicators to measure the therapeutic effect of aspirin 300 mg / day as a treatment associated with mechanical compression of the varicose ulcer. **You have the results in Jamovi. For NNT compute it by 1/ARR (Difference in proportions)** Or you can use: <https://statpages.info/ctab2x2.html> or <https://www.graphpad.com/quickcalcs/NNT1.cfm>). Format the results so that they accurately present both the point estimate of the medical indicator and its confidence interval (in the format: *point estimate (95% CI lower limit-upper limit)* - for details see examples in the *Interpretations* file):

**ARR =**

**NNT= 1/ARR =**

**RR=**

G. **Graphical illustration of the association between the treatment type and the healing of varicose ulcers**: **You have the results in Jamovi.**

Figure 1. Frequency of varicose ulcer healing based on treatment type (place the title below)

### E. Graphic illustration of the association between treatment type and D1-D2:

Figure 2. Reduction of the diameter of varicose ulcers based on treatment type

### Interpretation of Results

### A. Intrpretation of the comparability of the studied groups:

### Has there been a significant difference between gender distribution in patients who received aspirin versus those who received a placebo?

### Has there been a significant difference between the mean baseline diameter of the reference ulceration in patients who received aspirin versus those who received a placebo?

### Motivate your answer:

### Note the difference between the mean diameters of the two groups (in mm):

### *Conclusion on initial comparability*: were the samples comparable before the study?

### B. Interpretation of the results from a statistical point of view:

### B1. Reduction of the diameter of the reference varicose ulcer

### Null hypothesis regarding the diameter reduction of the reference varicose ulcer:

### H0:

### Alternative hypothesis regarding the diameter reduction of the reference varicose ulcer:

### H1:

### Null hypothesis rejected (yes / no). Explain why:

### Write the difference between the mean diameter reduction of the reference varicose ulcer in the two groups (in mm):

### B2. Healing

### Null hypothesis for varicose ulcer healing:

### H0:

### Alternative hypothesis for varicose ulcer healing:

### H1:

### Null hypothesis rejected (yes / no). Explain why:

### B3. Point estimates

### Interpretation of the point estimate of ARR:

### ARR=

### Interpretation of the 95% confidence interval of the above ARR:

### (95% CI - )

### Interpretation of the point estimate of NNT:

### NNT=

### C. Interpretation of results from a clinical point of view:

### C1. Clinically appreciate the difference in millimeters between the mean reduction of the reference ulcer diameter in the two groups (very important / moderate / less important):

### C2. Evaluate the size of ARR in clinical context (very important / moderate / less important):

### C3. Evaluate the size of NNT in clinical context (very important / moderate / less important):

### C4. Evaluate the size of RR in clinical context (very important / moderate / less important):

### C5. Evaluate the Accuracy of ARR based on the width of its confidence interval (broad range - imprecise results, narrow range - accurate results):

### C6. Interpret the confidence interval of ARR from clinical point of view (clinically important link - if both ends are clinically important; relatively little clinical importance - if both ends are of little clinical importance; or clinically unclear link - if one end of the 95% CI has a clinically significant value and the other is not important):

### D. Causality assessment:

### Assuming that this experimental study has succeeded to adequately control all sources of bias (systematic error) and confounders, can we conclude that there is a causal link between associating aspirin in a dose of 300 mg / day to mechanical compression of the affected limb for 24 weeks, and a superior healing effect of the varicose ulcer of the lower limb? (Yes / No) *Justify your answer:*

## To be retained

How do we recognize a randomized controlled clinical trial (RCT)?

* **experimental study** on volunteer human subjects, conducted under very rigorous methodological and ethical conditions
* it **compares the effects of an experimental treatment with those of a control treatment** (placebo in the case of a superiority trial or a reference treatment in a non-inferiority trial)
* all studied subjects have the same inclusion / exclusion criteria
* the compared **treatments are randomly allocated** to a **representative sample** extracted from the target population, without a known grouping of subjects imposed by the researcher
* Clinical trials apply **methods to minimize bias and confounders**: randomization, masked allocation, blinding, intention-to-treat analysis, adjustment analysis for variables with possible confounding role in the occurrence of the studied effect
* a clinical trial investigates links between a treatment and its effects; if methods of protection against bias and confounders are correctly applied, a **clinical trial can even demonstrate** these links at a causal level between the treatment and its evaluated effect.