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Review Article

Adequate use of biostatistics in biopharmacy and clinical studies: Critical elements and types of products studied

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Abstract

Background: Biostatistics are often used incorrectly in clinical studies of different types of products such as drugs, medical devices or dietary supplements. The safety and efficacy of the studied products is affected by such inappropriate use of biostatistics.

Methods: This analysis is a review of several studies, showing the risks of using biostatistics incorrectly, as well as the misinterpretation of the data that may occur. The proper proceedings in the pre-study phase and post-study analytical phase are presented.

Conclusions: These elements have major impacts on the development of clinical trials, regardless of the type of product investigated.

Introduction

Medicines, medical devices and dietary supplements are studied in clinical trials on human subjects to demonstrate their safety and efficacy [1]. When we talk about the statistical planning of clinical studies, we look first at the elements that may impact safety and efficacy, more specifically, the composition of the products, their indication, the therapeutic area covered, and the criteria for the inclusion and exclusion of the participating subjects [2]. Considering that there are clearly regulated differentiations between medicines [3], medical devices [4] and dietary supplements [5], this analysis aims to evaluate the appropriate use of statistical techniques for each category mentioned above: medicines, medical devices and dietary supplements.

Medicines either contain chemically synthesized substances or are biological products; therefore, the statistical technique used must be extremely rigorous in terms of first the safety and then the efficacy of the product (e.g., the Ipilimumab study [6]).

Medical devices are differentiated from medicines in that they produce a mechanical barrier (biofilm type) and have no pharmacodynamic action. Often, these devices contain a macromolecule (xyloglucan) and several plant extracts. Thus, the statistical technique used will take a different approach in terms of the methodology and the necessary sampling for this class of products (e.g., the Aprotecol versus Degasil study [7]).

Last but not least, dietary supplements have different regulations, as they are much more easily accepted on the market than medicines and medical devices. Therefore, the sampling and statistical methodology might take another approach in a study of dietary supplements (e.g., the Plantagyn study [8]), which use standardized quantities of herbal substances that do not exceed the legal limits.

The appropriate use of biostatistics in the above-presented cases would take into account the type of product (medicines, medical devices, dietary supplements), the composition of the product, the objectives of the study (safety and/or efficacy), and the budget that should be allocated for the study. In addition, the statistical methodology would have to be adapted to both the sampling approach and the analytical approach used in each type of study.

Appropriate and appropriate use of biostatistics in biopharmacy and clinical studies

There are multiple elements that contribute to the choice of certain working hypotheses, statistical tests and statistical power. In the following, we conduct a common analysis between medicines, medical devices and dietary supplements to show which common elements contribute to the design of a clinical study and which common elements may determine the inappropriate use of biostatistics.

The criteria underlying the decision to use a particular studio design are listed below. The enumeration is not exhaustive, but it represents the key elements that influence the design of a clinical study in the planning phase. These elements are common regardless of the type of product on which the clinical trial is conducted (Table 1).

The statistical methods, hypotheses and tests used in clinical studies depend on a series of assumptions that underlie the statistical method used in a clinical study [9].

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Common elements in the design of a clinical study	Medicines	Medical Devices	Dietary Supplements
Composition of the product	x	x	x
Therapeutic area	x	x	x
Objectives of the study	x	x	x
Inclusion and exclusion criteria	x	x	x
Status of ingredients (new/known)	x	x	x
Status of the product on the market	x	x	x
Type of design: double blind, single blind, open	x	x	x
Type of study: noninferiority, superiority, equivalence	x	x	x
Type of comparator: active/placebo	x	x	x

Table 1: Common criteria for establishing the study design and, implicitly, the statistical plan and the relevant statistical methods.

Critical elements that influence statistical methods in clinical studies	Medicines	Medical Devices	Dietary Supplements
Unrealistic statistical hypotheses	x	x	x
Inappropriate use of tests (parametric vs. nonparametric)	x	x	x
Sampling type (random, consecutive)	x	x	x
Allocation to therapy (randomized, consecutive)	x	x	x
Increased dropout rate of subjects	x	x	x
Misinterpretation of p values	x	x	x
Misinterpretation of confidence interval values	x	x	x
Misinterpretation of statistical power	x	x	x

Table 2: Critical elements that contribute to the inappropriate use of biostatistics in clinical trials.

Planning phase of the clinical trial	Analysis phase of the results of the clinical trial
Unrealistic statistical hypotheses	Increased dropout rate of subjects
Inappropriate use of statistical tests (parametric vs. nonparametric)	Misinterpretation of p values
Sampling type (random, consecutive)	Misinterpretation of confidence interval values
Allocation per therapy	Misinterpretation of statistical power

Table 3: The critical present study and poststudy elements that impact the statistical methodology.

		Reality	
		H_0 (there are no differences between groups)	**H_1 (there are differences between groups)**
Decision	**H_0 is rejected (if there are differences between groups)**	Type I error	X Test power
	H_0 is not rejected (if there are no differences between groups)	X	Type II error

Table 4: Correct decisions and errors in testing hypotheses.

The elements needed to calculate the sample required in a clinical trial
Effect size
Type 1 error
Type 2 error
Standard deviation

Table 5: Elements needed to calculate sampling.

Sampling type	**Form of application**
Sampling for an average, normal distribution	$N = \frac{(Z_\alpha + Z_\beta)^2 \times \sigma^2}{\delta^2}$
Sampling for 2 environments, quantitative data	$N = \frac{(Z_\alpha + Z_\beta)^2 \times \sigma^2}{\delta^2}$
Sampling for 2 proportions, categorical data	$N = \frac{4 \times (Z_\alpha + Z_\beta)^2}{\delta^2}$

Table 6: Elements needed to calculate sampling.

Prior to the clinical trial	**During the clinical trial**
The complexity of the interventions provided in the study protocol	Limited communication between investigator and subject
Established duration for the clinical trial	Lack of support offered to the subject during the study participation
Difficult inclusion and exclusion criteria	Wrong perception of the patient regarding participation in the clinical trial
Recruitment of less cooperative subjects	Influence and impact of the external environment: social, economic, religious, etc.
Lack of the provision of compensation for expenses (transport, accommodations, meals) associated with participation in the study	Too-high costs associated with participating in the clinical study and the lack of compensation or the existence of minimum compensation that does not cover the actual costs (Alexander, 2013)

Table 7: Critical elements that determine the dropout rate increase in clinical trials.

Prior to the clinical trial	During the clinical trial
Wrong sampling	Applying the statistical tests established in the study protocol
Overestimated effect size	Only p values lower than 0.001 should be treated as representing a finding in the clinical trial (Colquhoun, 2014)
Low-power experiment (under 80%)	Correct hypothesis testing: In the classic hypothesis testing with p = 0.05, those experiments that result in a p value less than or equal to 0.05 are considered significant
Selection of the applicable statistical tests	Limiting the intervention with statistical adjustment techniques in the data obtained
Avoidance of selection/ allocation bias of treatment	Testing for false-positive risk

Table 8: Critical elements in the correct interpretation of p values.

Wrong interpretation	Correct interpretation
95% CI contains the real population average	95% CI refers to the method used
95% CI contains 95% of the population data in this range	95% CI does not overlap with 95% of the normal distribution
95% CI contains 95% of the sample averages that fall into this range	95% CI: 95% of the sample averages fall outside this confidence interval
95% CI is the only source of error in the clinical trial	95% CI contains, in addition to the margin of error, other elements such as incorrect design of the study, selection bias, etc.

Table 9: Critical elements in the correct interpretation of p values.

Effect size (the minimum deviation from the null hypothesis that is desired to be detected)
Alfa (=0.05)
Beta (20%)
Standard deviation (obtained from the literature)

Table 10: The parameters used in the power analysis.

Effect size and estimated sample
The statistical method used
Reduction of measurement errors
Design of the study
Use of Bayesian methods

Table 11: Critical elements in the interpretation of statistical power (Dumas-Mallet et al., 2017).

The statistical method in practice is a mathematical representation of data variability [10].

Misinterpretation and misuse of statistical tests have been listed in multiple scientific journals that discourage the use of "statistical significance" or, more specifically, the limitation to p value when analyzing results as significant [11].

Interpretation issues of data obtained from clinical trials arise when there is an incomplete understanding of what p values, confidence intervals and power calculations mean [12]. Table 3 shows the critical elements that contribute to the inappropriate use of biostatistics in clinical trials. Therefore, the elements that may lead to the inappropriate use of biostatistics can be classified into 2 categories: preclinical study (planning phase and clinical trial design) and postclinical study (interpretation phase of the obtained results). Table 3 shows the prestudy and poststudy elements that impact the statistical methodology.

Planning phase of the clinical trial – the pre-study phase

Working hypothesis: There are 2 types of errors that can be made when testing a hypothesis: 1) rejecting the null hypothesis when it is true, which leads to the erroneous interpretation that there is a difference, even though a difference does not exist, and 2) not rejecting the null hypothesis when it is false, which leads to the erroneous interpretation that there are no differences, even though differences do exist [13].

According to Table 4, the cases marked with "x" represent the correct decisions: the null hypothesis is rejected when there is a difference ("test power"). The bottom left is the case of the null hypothesis being maintained when there are no differences.

Inappropriate use of statistical tests (parametric vs. nonparametric): There is a common practice in which parametric tests are not applied to data with non-normal distributions. Several studies have shown that the Mann-Whitney test generally has a higher power than the t-test unless the data are taken from normal [14]. In the case of randomized, double-blind clinical trials, we are interested in observing how certain variables change after treatment. A correct result is the replacement of the t-test with analysis of covariance (ANCOVA). ANCOVA is the preferred method of analyzing randomized trials with baseline and post-treatment measurements and is superior to the Mann-Whitney test. The recommendation is to use the ANCOVA method for randomized trials instead of the t-test (parametric) or Mann-Whitney test (nonparametric) (Figure. 1).

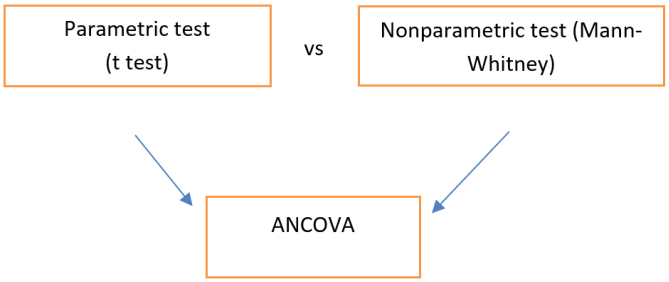

Figure 1: Using ANCOVA in randomized clinical trials is preferable to using a t-test or Mann-Whitney test.

Type of sampling: The main objective when calculating and justifying the sampling for a clinical trial is to determine the number of participants needed to detect a relevant effect of the treatment used. Table 5 shows the elements needed to calculate sampling while Table 6 shows few sampling formulas. The greater the variability, the larger the selected sample must be [15].

Allocation to therapy: Inappropriate allocation of subjects to therapy may lead to exaggeration of the effects of treatment in some studies and underestimation of the effects in others [16]. The elements to be avoided when allocating treatment are presented in Figure. 2.

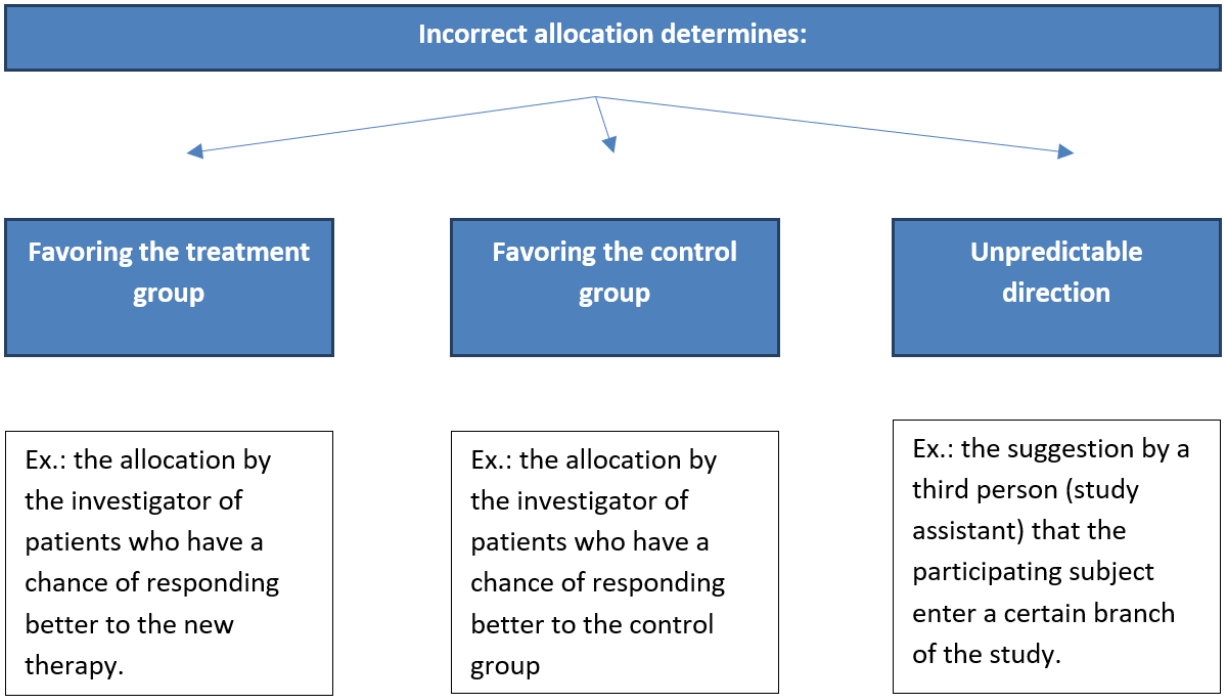

Figure 2: Inadequate allocation to study therapy.

Phase of analysis of the results of the clinical trial – the postclinical trial stage

Increased dropout rate of subjects: Dropout is a serious problem for any randomized study because it can compromise statistical power due to lack of data [17]. A subject must be in the study long enough to participate in the interventions described in the study protocol. According to the legislation currently in force, subjects may at any time forgo participation in the clinical trial, but the study will then be unable to generate data on the interventions on which it is based. So-called missing data are generated, which lead to unrealistic correlations regarding the response of the subject to the treatment in the situation in which he/she withdrew from the study earlier than specified in the research protocol. Table 7 shows the critical elements that determine the dropout rate. Ideally, each subject should generate data according to the procedures described in the protocol [18].

Misinterpretation of p values: P values between 0.01 and 0.05 resulting from the statistical analysis are often considered statistically significant. However, what if this result is a false positive? [19]. What should be considered in order to not misinterpret a p value as statistically significant? The probability that the results of the research will occur at random is associated not with the p value but with the false-positive risk [20]. Table 8 shows the critical elements in the correct interpretation of p values.

Misinterpretation of the confidence interval values: Confidence intervals are key to inferential statistics. We can use probabilities and information from a probability distribution to estimate a population parameter with the use of a sample. Specifying a confidence interval is done in such a way that it can be easily understood. Table 9 shows the critical elements in interpreting confidence intervals [21].

Misinterpretation of statistical power: The lack of adequate power causes many studies to be inconclusive in detecting even large differences between groups. Moreover, a lack of statistical power may induce false conclusions that subsequently influence the clinical behavior of physicians. In the sampling stage, power calculations must provide a sufficient pool of patients to achieve clinically meaningful results. Table 10 shows the parameters used in the power analysis and Table 11 shows critical elements in the interpretation of statistical power [22].

Conclusions

The critical elements mentioned in this analysis are found in 2 major stages of the life cycle of a clinical study: 1) the study planning stage and 2) the study phase. These elements have a major impact on the development of clinical trials, regardless of the type of product investigated. Addressing these critical elements in the most appropriate way could greatly reduce the false-positive results obtained in clinical trials and improve current medical practice. This analysis is limited to the revised articles and the author's personal practice. Certainly, more research is needed to configure a specific framework for the adequate use of biostatistics in clinical trials.

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