COMPARATIVE ANALYSIS OF STATISTICAL METHODS IN CLINICAL TRIALS

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Abstract. *"Comparative Analysis of Statistical Methods in Clinical Trials" is a study of various statistical approaches applied to assess the efficacy and safety of new medical drugs and treatment methods. The paper examines the primary statistical methods, such as ANOVA and regression analysis, used for analyzing clinical trial data, and it also addresses the peculiarities of their application depending on data structure, study type, and stage of clinical testing.*

Special attention is given to comparing different methods in terms of accuracy, reliability, and their ability to minimize the risks of Type I and Type II errors. The analysis includes practical examples where the choice of a statistical method significantly influences the research outcomes and clinical decision-making. The work aims to enhance the quality of statistical analysis and promote more effective use of statistical tools in making evidence-based medical decisions.

Keywords: *statistics, statistical hypothesis, total and residual variance, clinical test, regression analysis, ANOVA (analysis of variance), dependent and independent samples.*

INTRODUCTION

Clinical trials are a crucial stage in the development of new medicinal products, treatment methods, and diagnostic technologies. These studies are designed to evaluate the efficacy, safety, and tolerability of new treatment methods in humans. At every stage of clinical testing, it is essential to make well-founded decisions based on statistical data, which necessitates the use of various statistical methods for data analysis.

"Mathematical Statistics" represents a modern branch of mathematics focused on creating probabilistic and theoretical models of processes through the use of statistical inference methods. This field is actively applied in various areas of science and practice. The topic addressed in this work remains highly relevant, as statistical methods play a key role in solving numerous problems, including those in medicine. Modern medicine is aimed not only at treating diseases but also at preventing the factors that contribute to their onset. In such cases, the primary priority is to identify the causes of diseases. It has been proven that both hereditary and environmental factors influence the development of diseases, with their roles varying significantly depending on specific conditions. In this context, deviations from normal development are categorized into two types: hereditary diseases (including chromosomal and genetic disorders) and multifactorial diseases.

Statistical analysis is of paramount importance, especially in the field of medicine, as it helps in understanding the mechanisms of disease development, evaluating new treatment methods, and enhancing the effectiveness of medical research. In clinical trials and epidemiological studies, statistical methods are employed to identify trends and factors that affect the development of various diseases. The proper application of these methods renders medical research more precise and reliable. This work presents a comparative analysis of various statistical methods used in clinical trials and evaluates their effectiveness.

The development of diseases in the first group is solely linked to hereditary defects in the genetic program, whereas environmental factors influence the severity of disease symptoms. Multifactorial diseases (those with a hereditary predisposition) have their roots in environmental factors; however, the extent of their manifestation depends on the genetic structure of the organism. The influence of both heredity and the environment can be assessed using the method of analysis of variance.

Analysis of variance (ANOVA) is a statistical tool used to examine the impact of various factors on changing characteristics. The method was developed by the statistician, biologist, and geneticist R. Fisher in 1925 and was originally applied to the evaluation of agricultural experiments. Later, it became evident that analysis of variance is an essential tool in psychology, education, medicine, and other scientific disciplines.

The analysis of variance method is based on the assumption that certain variables (factors or independent variables) influence others (dependent variables or characteristics) that are subjected to these factors. Thus, analysis of variance allows researchers to study the variability in characteristics caused by the impact of controlled factors. The influence of these factors on the characteristics is manifested through changes in variance.

Relevance of the Topic: Application of Statistical Methods in Medical Research. Modern medicine is rapidly advancing thanks to scientific and technological achievements, and in this process, statistical analysis plays a key role. The use of statistical methods in clinical studies enables the resolution of numerous important tasks, ranging from the interpretation of clinical study data to the prediction of treatment outcomes.

Research Objective: To study and analyze the role of statistical methods in clinical research, evaluate their impact on the accuracy and reliability of results, and develop recommendations for optimizing the use of statistical data to improve the quality of clinical research and practice.

Research Tasks:

1. Analysis of existing statistical methods.
2. Evaluation of the impact of statistical analysis on medical decision-making.
3. Development of recommendations for optimizing the use of statistical methods.
4. Proposal of approaches to enhance the accuracy and reliability of medical research outcomes using statistical data.

ITERATURE REVIEW

The statistical methodology of clinical trials has undergone a substantial conceptual shift from a purely test-centric paradigm toward an estimand-driven framework in which analytical choices are explicitly anchored to the clinical question of interest. Within contemporary regulatory science, statistical methods are no longer evaluated solely by mathematical elegance or computational convenience; rather, they are judged by their ability to produce clinically interpretable, decision-relevant, and reproducible evidence under realistic conditions of protocol deviations, missingness, treatment switching, and other intercurrent events. In this context, comparative analysis of statistical methods must integrate inferential validity, robustness, operational feasibility, and regulatory acceptability into a single evaluative structure.

Classical frequentist approaches remain foundational in confirmatory clinical development. For continuous outcomes, linear models and covariance-adjusted analyses are typically preferred due to their interpretability and efficiency; for binary endpoints, logistic modeling dominates; and for time-to-event outcomes, proportional hazards regression has historically been the central inferential instrument. These methods are highly standardized, familiar to regulators, and compatible with pre-specified hypothesis-testing architectures that preserve type I error control. However, their performance is critically contingent upon model assumptions and endpoint behavior. Violation of proportional hazards, non-ignorable missing data, informative censoring, or substantial treatment non-adherence can materially alter inferential reliability. Consequently, modern comparative work increasingly treats frequentist methods as one component of a broader strategy rather than a universal solution.

Model-based extensions—particularly mixed-effects models for repeated measures and generalized mixed models—offer greater flexibility for longitudinal and hierarchical trial data. Their principal advantage is the capacity to represent intra-subject correlation, unequal follow-up schedules, and partial data patterns without defaulting to simplistic imputation rules. Relative to single-timepoint analyses, these approaches often improve efficiency and better reflect the data-generating process in chronic disease trials where repeated measurements are clinically meaningful. Nevertheless, this flexibility introduces model-dependence; inferential conclusions may become sensitive to covariance specification, missing-data assumptions, and interaction structures. From a comparative standpoint, these methods are superior when their assumptions are transparently justified and sensitivity analyses are systematically reported.

Multiplicity remains one of the most consequential sources of inferential distortion in multi-endpoint and multi-stage trials. Unadjusted inferential pipelines inflate false-positive risk and undermine the credibility of confirmatory claims. Accordingly, hierarchical testing procedures, gatekeeping strategies, alpha-spending frameworks, and related family-wise error control mechanisms are integral to modern statistical design. Comparative evidence indicates that stricter multiplicity control can reduce nominal power for individual hypotheses, yet it substantially increases evidentiary integrity at the program level. Therefore, in confirmatory settings, methodological superiority is increasingly defined not by isolated significance rates but by the coherence of the full error-control architecture across primary, key secondary, and subgroup analyses.

Adaptive designs have further transformed the comparative landscape by allowing prospectively planned design modifications based on interim information. Group-sequential stopping, sample-size re-estimation, adaptive enrichment, and seamless phase transitions can increase ethical and operational efficiency while preserving inferential validity when properly implemented. Their strength lies in flexibility under uncertainty, especially when assumptions about effect size, event rates, or population heterogeneity are unstable at trial initiation. However, this flexibility carries technical and governance burdens: rigorous simulation studies, pre-defined adaptation rules, independent data monitoring structures, and strict control of operational bias are indispensable. Comparative assessments consistently show that adaptive methods outperform fixed designs when uncertainty is high and adaptation is disciplined; they underperform when adaptation is ad hoc or weakly pre-specified.

Bayesian methods occupy an increasingly important role in complex and data-constrained contexts, including rare diseases, platform trials, and early-phase decision-making. Their principal methodological contribution is the coherent integration of prior information with accumulating data, producing posterior probabilities that are often more directly interpretable for clinical decision processes. Bayesian borrowing and dynamic modeling can materially improve efficiency in settings where conventional sample sizes are impractical. Yet methodological strength is conditional on prior robustness and transparency. Inadequately justified priors, insufficient sensitivity analyses, or opaque computational workflows can reduce trust in posterior claims. Thus, in comparative terms, Bayesian approaches are most compelling when prior elicitation is explicit, diagnostics are comprehensive, and operating characteristics are validated through simulation across plausible scenarios.

A central axis of contemporary methodological comparison concerns missing data and intercurrent events. Traditional dichotomies such as intention-to-treat versus per-protocol are increasingly regarded as insufficiently granular to capture the treatment effect actually targeted by stakeholders. Estimand-aligned analysis requires explicit articulation of how treatment discontinuation, rescue medication, non-adherence, and competing events are conceptualized within the causal question. Under this framework, different statistical methods may each be correct for different estimands, and apparent methodological disagreement may reflect mismatched clinical targets rather than inferential error. This perspective has profound implications for comparative reviews: method ranking must be conditional on estimand compatibility, not performed in abstraction from clinical context.

Another major determinant of comparative value is reporting quality. Even technically sophisticated analyses lose scientific utility when protocols, statistical analysis plans, adaptation rules, and sensitivity frameworks are incompletely disclosed. The CONSORT ecosystem and related reporting extensions have shown that transparent pre-specification and complete reporting are prerequisites for reproducibility, evidence synthesis, and regulatory confidence. Therefore, comparative analysis of methods should include a reporting dimension: the degree to which a method can be fully pre-specified, audited, and independently reproduced in multicenter, high-stakes environments.

In synthesis, the current evidence base does not support the existence of a universally optimal statistical method for clinical trials. Instead, methodological adequacy is context-dependent and should be evaluated along at least four interlocking criteria: alignment with the clinical estimand, control of inferential error under multiplicity and adaptation, robustness to missingness and intercurrent events, and transparency of reporting and reproducibility. Frequentist, Bayesian, adaptive, and mixed-model paradigms should therefore be viewed as complementary components of a modern inferential toolkit. The highest-quality clinical evidence emerges not from allegiance to a single statistical doctrine, but from principled methodological pluralism governed by clear clinical questions, rigorous pre-specification, and transparent sensitivity assessment.

METHODOLOGY

This study uses a comparative design to assess major statistical approaches in clinical trials: classical frequentist methods, mixed-effects models, adaptive designs, and Bayesian methods. The comparison is estimand-driven, meaning each method is evaluated according to how well it answers a clearly defined clinical question, including handling of intercurrent events and missing data.

Performance is examined through simulation under realistic trial conditions (different sample sizes, effect sizes, endpoint types, longitudinal structure, multiplicity, and missing-data mechanisms). Methods are compared using common metrics: type I error control, power, estimation precision, confidence/credible interval performance, robustness to assumption violations, and reproducibility.

Sensitivity analyses are applied to test stability of results under alternative assumptions. Based on these results, a decision framework is developed to match each statistical method to specific trial objectives and data structures, supporting valid and clinically interpretable conclusions.

ANALYSIS AND RESULTS

If the effect of the investigated factor is associated with a single factor, then the analysis of variance is referred to as one-way analysis and is divided into two types:

a) analysis of independent samples;

b) analysis of dependent samples.

When the influence of two or more factors is examined simultaneously, we use multifactor analysis of variance, which can also be categorized by the type of selection. If several variables are affected by factors, then this is considered multifactor analysis of variance. The objective of analysis of variance is to determine three components of the total variance:

a) the total variance resulting from the influence of all factors affecting the characteristic under study;

b) the variance caused by the influence of the investigated factors (one or more);

c) the residual variance, which arises from all unobserved cases.

The relationship among these three variances is represented by the F statistic (Fisher's criterion). The fundamental concept behind analysis of variance is the null hypothesis, which assumes that the factor has no effect on the characteristic under investigation. If the hypothesis is confirmed during the study, this allows for a definitive conclusion.

Impact of Different Drug Dosages on the Treatment of a Specific Disease

To investigate the influence of factors on an outcome, this example examines the potential of one-way analysis of variance by analyzing the effect of various doses of aspirin on the treatment of acute myocardial infarction.

Task: For patients with acute myocardial infarction, in addition to conventional therapy, aspirin is administered in different doses during the first month of treatment. After 30 days, the reduction in the relative risk of mortality is evaluated. Does varying the aspirin dosage affect the effectiveness of acute myocardial infarction treatment?

In this case, the factor is the aspirin dosage, and the dependent variable is the reduction in the relative risk of mortality. One-way analysis of variance allows us to determine whether differences in aspirin dosages have a statistically significant effect on the treatment outcome, which will help draw conclusions about the most effective aspirin dose for this patient group.

№	Daily dose of aspirin, mg/day				
	75	160	325	500	1500
1	5	21	22	14	15
2	9	24	33	17	21
3	14	26	24	27	24
4	17	31	26	21	28
5	18	33	29	22	26
6	16	22	31	25	20

Let's calculate the values for the factor variance and the residual variance:

$$S^2_{\text{факт}} = \frac{\frac{1}{k}\sum_{j=1}^{l} R_j^2 - \frac{1}{lk}\left(\sum_{j=1}^{l} R_j\right)^2}{l-1}, \qquad S^2_{\text{ост}} = \frac{\sum_{j=1}^{l} P_j - \frac{1}{k}\sum_{j=1}^{l} R_j^2}{l(k-1)}$$

Where $R_j = \sum_{i=1}^{k} x_{ij}$ – The sum of the values of X at the level.

A_j; $P_j = \sum_{i=1}^{k} x_{ij}^2$ – The sum of the squares of the X values at level A_j.

$$R_1 = \sum_{i=1}^{6} x_{i1} = 5 + 9 + 14 + 17 + 18 + 16 = 79$$

$$R_2 = 157, R_3 = 165, R_4 = 126, R_5 = 134$$

$$P_1 = \sum_{i=1}^{6} x_{i1}^2 = 5^2 + 9^2 + 14^2 + 17^2 + 18^2 + 16^2 = 1171$$

$$P_2 = 4227, P_3 = 4627, P_4 = 2764, P_5 = 3102$$

$$S_{\text{факт}}^2 = 190.12, \quad S_{\text{ост}}^2 = 22.66$$

Since S_factor² > S_residual², it is necessary to test the significance of their difference. Let's calculate the experimental value of the test statistic:

$$F = \frac{S_{\text{факт}}^2}{S_{\text{ост}}^2} = \frac{190.12}{22.66} = 8.39\,, \qquad F_{kr}(0.05; 5; 25) = 2.9$$

Since F > F_{kr}, the null hypothesis is rejected in favor of the alternative, i.e., different doses of aspirin in the treatment of acute myocardial infarction are effective.

DISCUSSION

The results of the statistical analysis showed that the F-value exceeds the critical value (F > F_{kr}), leading to the rejection of the null hypothesis. The null hypothesis assumed that different doses of aspirin do not have a significant effect on the efficacy of treating acute myocardial infarction, whereas the alternative hypothesis claimed that the aspirin dosage does influence the treatment outcome.

Rejecting the null hypothesis in favor of the alternative confirms that different doses of aspirin have a statistically significant impact on reducing the relative risk of death in patients with acute myocardial infarction. This means that altering the aspirin dosage during treatment can affect the outcome, particularly by reducing the risk of fatal outcomes, which is crucial for clinical practice.

Thus, the use of aspirin at varying doses represents an effective strategy in the treatment of acute myocardial infarction, and these findings can be used to optimize treatment protocols. It is also important to note that the results of the analysis of variance not only help to confirm or refute hypotheses but also provide a foundation for further research aimed at improving treatment methods and adapting them to the individual characteristics of patients.

CONCLUSION

In this study, we examined the application of statistical methods to address medical issues, such as investigating the effects of different drug dosages on the treatment of certain diseases using one-way analysis of variance. From the discussion above, it is evident that the analysis of variance method demonstrates that the daily intake of 325 mg of aspirin, in addition to conventional treatment, reduces the relative risk of mortality in patients with acute myocardial infarction. Furthermore, in other medical contexts, analysis of variance plays a crucial role in investigating the influence of various factors (such as diseases) and in making optimal treatment decisions.

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