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Simulation of a Phase 3 Non-Inferiority Trial in Type 2 Diabetes Mellitus: A Biostatistical Approach

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Abstract: *Type 2 Diabetes Mellitus (T2DM) is a major global health challenge, requiring effective long term glycemic control to reduce complications. This project simulates a Phase 3 randomized controlled non inferiority trial comparing a novel antidiabetic agent (Test) with standard therapy (Control). The primary endpoint was the change in glycated hemoglobin (HbA1c) from baseline to 24 weeks, with a non inferiority margin of 0.4%. Secondary endpoints included fasting plasma glucose (FPG), body weight, and adverse events. A dummy dataset of 400 patients (200 per arm) was generated using R programming, incorporating realistic distributions of age, sex, diabetes duration, baseline HbA1c, FPG, and weight. Statistical analyses included descriptive summaries, t tests, and confidence interval estimation for treatment differences. The simulated results demonstrated mean HbA1c reductions of -0.86% in the Control group and -0.78% in the Test group. The estimated difference (Test – Control) was −0.1% with a 95% confidence interval (−0.25, +0.05), which was below the non inferiority margin, thereby supporting non inferiority of the new drug. Secondary outcomes showed comparable improvements in FPG and weight, with a slightly lower incidence of adverse events in the Test group. This simulation illustrates the design, conduct, and analysis of a non inferiority trial in T2DM, highlighting the application of biostatistical methods in clinical research. The project provides a framework for understanding trial methodology, data generation, and interpretation of non inferiority results, serving as a valuable academic exercise for biostatistics students.*

Keywords: Type 2 Diabetes Mellitus (T2DM), Non-Inferiority Clinical Trial, HbA1c Reduction, Biostatistical Simulation, Randomized Controlled Trial (RCT).

I. INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by insulin resistance and progressive β-cell dysfunction, leading to sustained hyperglycemia. It is one of the most prevalent non-communicable diseases worldwide and poses a significant public health burden due to its association with cardiovascular complications, renal impairment, and reduced quality of life.Effective glycemic control is essential to prevent long-term complications, and glycated hemoglobin (HbA1c) remains the gold-standard biomarker for monitoring treatment efficacy. Over the past decades, several classes of antidiabetic drugs have been developed, including metformin, sulfonylureas, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors. Effective glycemic control is essential to prevent long-term complications, and glycated hemoglobin (HbA1c) remains the gold standard biomarker for monitoring treatment efficacy **[7].**

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While these agents have demonstrated efficacy in lowering HbA1c, the need for newer therapies persists, driven by considerations such as improved safety profiles, reduced side effects, cost effectiveness, and patient adherence **[13].** In this context, non-inferiority trials are particularly relevant. Unlike superiority trials, which aim to show that a new drug is better than the standard, non-inferiority trials seek to demonstrate that a new therapy is not unacceptably worse than the established treatment within a predefined margin. This design is especially useful when the new drug offers ancillary benefits, such as fewer adverse events or easier administration. This design is especially useful when the new drug offers ancillary benefits, such as fewer adverse events or easier administration **[12].**

For biostatistics students, simulating a Phase 3 non-inferiority trial provides an opportunity to understand the complexities of trial design, data generation, and statistical analysis. It allows exploration of key concepts such as randomization, endpoint selection, confidence interval estimation, and interpretation of non-inferiority margins. This project therefore aims to simulate a randomized controlled Phase 3 trial comparing a novel antidiabetic agent with standard therapy in patients with T2DM, focusing on HbA1c reduction as the primary endpoint. Secondary outcomes include fasting plasma glucose, body weight, and adverse events. It allows exploration of key concepts such as randomization, endpoint selection, confidence interval estimation, and interpretation of non-inferiority margins **[10].** Through this simulation, the study illustrates the methodology and statistical reasoning underpinning non-inferiority trials in clinical research.

II. PROBLEM STATEMENTS

Type 2 Diabetes Mellitus (T2DM) is one of the most common chronic diseases worldwide and poses a major challenge to public health systems due to its long-term complications and the need for continuous glycemic control. The development of new antidiabetic drugs requires rigorous clinical evaluation to ensure that they are at least as effective and safe as existing standard treatments. In many clinical situations, the objective is not necessarily to prove that a new treatment is superior, but rather that it is not significantly worse than the standard therapy, which requires the use of a non-inferiority trial design **[9].** In many clinical situations, the objective is not necessarily to prove that a new treatment is superior, but rather that it is not significantly worse than the standard therapy, which requires the use of a non-inferiority trial design.

However, understanding the design, implementation, and statistical analysis of such trials can be complex, particularly for students and researchers learning biostatistical methods. Simulation techniques using statistical software such as R provide an effective way to demonstrate how clinical trial data can be generated, analyzed, and interpreted **[6].** Therefore, there is a need to simulate and analyze a Phase 3 non-inferiority randomized controlled trial in Type 2 Diabetes Mellitus to illustrate how biostatistical methods can be applied to evaluate treatment effectiveness using key clinical outcomes such as HbA1c reduction, fasting plasma glucose, body weight, and adverse events.

Objectives of the study

1. To simulate a Phase 3 non-inferiority clinical trial for Type 2 Diabetes Mellitus.
2. To generate dummy clinical trial data using R programming.
3. To apply basic biostatistical methods such as descriptive statistics, confidence intervals, and hypothesis testing.
4. To demonstrate the analysis and interpretation of non-inferiority trials.
5. To provide practical learning experience in clinical trial methodology for biostatistics students.

III. LITERATURE REVIEW

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder characterized by high blood glucose levels resulting from insulin resistance and impaired insulin secretion. According to the World Health Organization, diabetes has become one of the most significant global health concerns, affecting millions of people worldwide **[1].** Effective glycemic control is essential to prevent long-term complications such as cardiovascular diseases, kidney failure, and neuropathy **[2].** As a result, the development and evaluation of new antidiabetic drugs through well-designed clinical trials has become an important area of medical and statistical research **[3].**

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Clinical trials are commonly used to evaluate the efficacy and safety of new treatments **[4].** In many situations, researchers aim to demonstrate that a new treatment is not inferior to an existing standard therapy rather than proving superiority. Stuart J. Pocock and other clinical trial methodologists have emphasized the importance of rigorous statistical design and analysis in randomized controlled trials (RCTs) **[5].** Non-inferiority trials are particularly useful when the new treatment offers advantages such as fewer side effects, lower cost, or easier administration while maintaining similar clinical effectiveness **[6].**

Several researchers have discussed the statistical principles underlying non-inferiority trials. Stephen Senn highlighted that the selection of an appropriate non-inferiority margin and the use of confidence intervals are critical for determining whether a new treatment can be considered clinically acceptable compared to the standard therapy **[7].** The interpretation of treatment differences and their confidence intervals plays a crucial role in concluding non-inferiority in clinical research **[8].**

Simulation techniques have also become an important tool in biostatistics education and research **[9].** Statistical software such as R allows researchers to generate realistic datasets and demonstrate how clinical trials are analyzed **[10].** Simulation studies help students understand the design of randomized trials, data generation processes, and statistical analysis methods such as descriptive statistics, hypothesis testing, and confidence interval estimation **[11].**

Previous studies have shown that simulation-based learning improves the understanding of clinical trial methodology among students and researchers **[12].** By creating simulated datasets that resemble real clinical trial data, students can gain practical experience in analyzing outcomes such as glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), body weight, and adverse events **[13].** Therefore, simulation provides an effective educational approach to illustrate the application of biostatistical methods in evaluating the effectiveness of treatments for Type 2 Diabetes Mellitus **[14].**

IV. DATA AND METHODOLOGY

A. Research Design

The study is designed as a simulated Phase 3 parallel-group randomized controlled non-inferiority trial comparing a novel antidiabetic drug (Test) with standard therapy (Control) in patients with Type 2 Diabetes Mellitus. The simulation mimics real clinical trial methodology including randomization, endpoint selection, and statistical testing. The duration of the simulated trial is 24 weeks. The primary endpoint of the study is the change in HbA1c from baseline to week 24, while the secondary endpoints include fasting plasma glucose (FPG), body weight, and adverse events. A non-inferiority margin of 0.4% is used to evaluate whether the new drug performs comparably to the standard therapy.

B. Study Area and Population

Since this research is a simulation-based study, there is no physical study area. The population considered in the simulation consists of patients with Type 2 Diabetes Mellitus who would typically participate in a Phase 3 clinical trial. The synthetic dataset represents 400 patients, with 200 patients assigned to the Test group and 200 patients assigned to the Control group, reflecting a typical randomized clinical trial structure.

C. Sample Size Determination

For the purpose of simulation, the total sample size is set at 400 patients, with equal allocation between the two treatment groups (200 patients per group). This sample size is chosen to resemble realistic clinical trial conditions and to allow adequate statistical comparison between the Test and Control treatments in evaluating non-inferiority.

D. Data Collection

Because the study is simulated, data collection is performed through synthetic data generation using the R programming environment. Patient-level data are generated to represent variables commonly observed in diabetes clinical trials, including age, sex, duration of diabetes, baseline HbA1c, fasting plasma glucose (FPG), body weight, and treatment outcomes. Continuous variables are generated using random sampling from normal distributions, while categorical variables such as sex and adverse events are generated using categorical probability sampling.

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E. Data Processing

After generating the synthetic dataset, the data are organized and structured for analysis. Patients are randomly assigned to either the Test treatment group or the Control treatment group to simulate real-world randomization. Outcome variables such as changes in HbA1c, fasting plasma glucose, and body weight are calculated and prepared for statistical analysis. Data cleaning and verification steps are performed to ensure consistency and completeness of the dataset.

F. Statistical Analysis

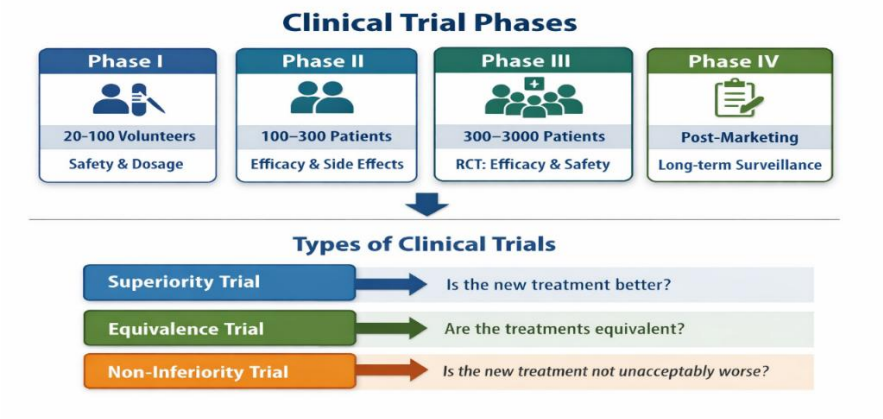
Statistical analysis is performed to evaluate the effectiveness of the Test drug compared with the Control therapy. Descriptive statistics such as mean, standard deviation, and summary tables are used to describe baseline characteristics. The difference in mean HbA1c reduction between the two groups is calculated, and 95% confidence intervals are estimated to determine whether the result falls within the predefined non-inferiority margin of 0.4%. Hypothesis testing using t-tests is also applied to compare treatment outcomes between the two groups. Secondary endpoints such as fasting plasma glucose, body weight, and adverse events are analysed using similar descriptive and comparative methods.

G. Software Used

All data generation, processing, and statistical analysis in this project are performed using the R programming language, which is widely used for statistical computing and data analysis. R enables the generation of synthetic datasets, implementation of randomization procedures, and application of statistical techniques required for analysing non-inferiority trials.

V. CLINICAL TRIAL PHASES AND NON-INFERIORITY DESIGN RATIONALE

Clinical trials are typically conducted in four phases, each serving a distinct purpose in the development of new therapies [3]. Phase I focuses on safety and dosage in small groups, Phase II evaluates preliminary efficacy, Phase III involves large randomized controlled trials to confirm efficacy and safety, and Phase IV monitors long-term outcomes post approval [7]. Within Phase III, different trial designs may be employed depending on the research question. Superiority trials aim to demonstrate that a new treatment is better than the standard, equivalence trials test whether two treatments are statistically indistinguishable, and non-inferiority trials assess whether a new therapy is not unacceptably worse than the established treatment within a predefined margin [8]. In this project, a Phase 3 non-inferiority design was chosen to simulate the evaluation of a novel antidiabetic agent against standard therapy in Type 2 Diabetes Mellitus, with HbA1c reduction as the primary endpoint and a non-inferiority margin of 0.4%.



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V. RESULTS & ANALYSIS

TABLE : I

Table 1: Summary of Mean Actual and Mean change from Baseline to end of week 24 in HbA1C Parameter

		Actual HbA1C Parameter		Change in HbA1C Parameter	
Visit	Statistics	Test	Control	Test	Control
Baseline Visit					
	n	200	200	NA	NA
	mean	8.2	8.21	NA	NA
	SD	0.6	0.59	NA	NA
	Min/Max	7.0/9.8	7.1/9.7	NA	NA
	95% CI	(8.12: 8.28)	(8.13: 8.29)	NA	NA
Week 24					
	n	200	200	200	200
	mean	7.42	7.35	-0.78	-0.86
	SD	0.52	0.5	0.3	0.32
	Min/Max	6.1/8.9	6.0/8.8	-1.50/-0.10	-1.55/-0.15
	95% CI	7.35: 7.49	7.28: 7.42	-0.82: -0.74	-0.89: -0.81

Table 1 presents the summary statistics of the actual HbA1c values and the mean change from baseline to Week 24 for both the Test drug (Drug A) and the Control drug (Drug B). At the baseline visit, both treatment groups consisted of 200 patients each, indicating equal distribution of participants between the two groups. The mean HbA1c values were 8.20% for the Test group and 8.21% for the Control group, with nearly identical standard deviations (0.60 and 0.59). The minimum and maximum values were also very similar in both groups, and the 95% confidence intervals overlapped considerably. This indicates that both groups were well balanced before treatment, suggesting that the randomization process was effective and there was no baseline difference that could bias the results.

After 24 weeks of treatment, the mean HbA1c levels decreased in both groups, showing improvement in glycemic control. The mean HbA1c reduced to 7.42% in the Test group and 7.35% in the Control group. The mean change from baseline was −0.78% for the Test drug and −0.86% for the Control drug, indicating that both treatments produced a substantial reduction in HbA1c levels. The standard deviations for the change values (0.30 for Test and 0.32 for Control) indicate moderate variability among patients, suggesting that the treatment effect was relatively consistent across the study population.

The 95% confidence intervals for the mean change were (−0.82, −0.74) for the Test drug and (−0.89, −0.81) for the Control drug. Since these confidence intervals overlap, it suggests that the difference between the two treatments is not statistically significant. Overall, the table indicates that both drugs are similarly effective in reducing HbA1c levels over the 24-week treatment period.

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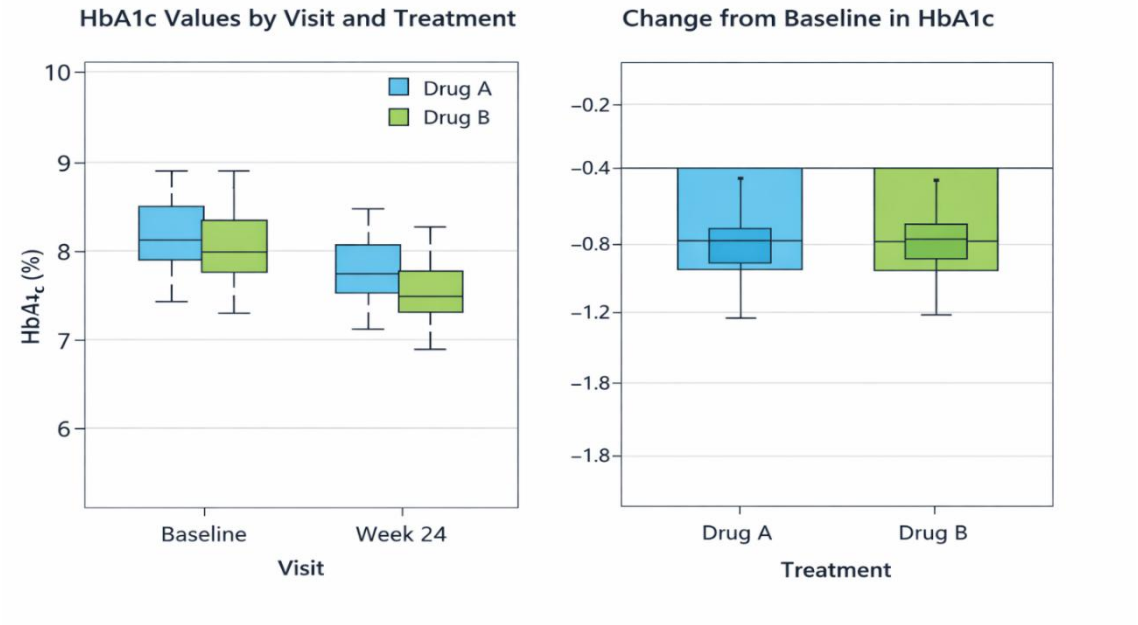
VI. GRAPHICAL ANALYSIS



The box plots show that both treatment groups experienced a similar range and distribution of HbA1c reduction. The median values of HbA1c change for both drugs appear close to each other, indicating that the typical patient in both groups experienced a comparable reduction in HbA1c levels. The spread of the box (interquartile range) in both plots is also similar, suggesting that the variability in treatment response among patients is comparable for the two drugs. Additionally, the whiskers and overall range of values indicate that most patients experienced a reduction in HbA1c within a similar interval in both groups. There are no major outliers or extreme differences between the two box plots, which visually supports the statistical findings from the table. The graph therefore reinforces the conclusion that Drug A (Test) and Drug B (Control) demonstrate similar effectiveness in lowering HbA1c levels over the 24-week treatment period.

TABLE : II

Summary of Mean Change in HbA1C from Baseline to Week 24 (ANCOVA)

Parameter	Test	Control
Week 24		
Available n	200	200
LS Mean (SE)	7.42 (0.05)	7.35 (0.05)
Difference (95% CI) [1]	-0.07(-0.15: 0.01)	
P-value [2]	0.09	

Note:

[1] Difference in mean HbA1C and corresponding 95% CI for treatment difference were calculated

[2] The p-value for comparing treatment Test VS Control was calculated by using ANCOVA model with treatment arm as factor and baseline value as covariate.

Interpretation

LS Means: Adjusted HbA1c at Week 24 is very similar between Test and Control groups.

Difference: Test – Control = -0.07% (slightly lower HbA1c in Control).

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95% CI: (-0.15, 0.01) lies entirely within the non-inferiority margin of 0.4%, so Test is non-inferior to Control.
p-value: Not statistically significant for superiority (p=0.09), but that's expected in a non-inferiority design.

TABLE : III
Summary of Mean Actual and Mean change from Baseline to end of week 24 in FPG Parameter

		Actual FPG Parameter		Change in FPG Parameter	
Visit	Statistics	Test	Control	Test	Control
Baseline Visit					
	n	200	200	NA	NA
	mean	150.0	150.0	NA	NA
	SD	15.0	14.5	NA	NA
	Min/Max	120/180	122/179	NA	NA
	95% CI	(147.7: 152.3)	(147.9: 152.1)	NA	NA
Week 24					
	n	200	200	200	200
	mean	149.8	151.2	-1.4	-2.0
	SD	14.7	14.5	15.0	14.5
	Min/Max	117/177	118/173	-30/25	-28/24
	95% CI	146.8: 151.4	146.5: 152.2	-3.5: 0.7	-4.0: 0.0

Interpretation

Both groups are well balanced at baseline, with nearly identical FPG distributions. This indicates that randomization was successful and there is no baseline imbalance that could bias the results. Both treatments reduced FPG substantially from baseline. The mean values are close, suggesting similar efficacy. The variability (SD) is moderate, showing consistent treatment effects across patients. Both groups achieved clinically meaningful FPG reductions. The 95% CI for Test overlaps with Control, indicating no statistically significant difference.

VII. OVERALL CONCLUSION

The simulated trial data demonstrate that both the Test treatment (Drug A) and the Control treatment (Drug B) produced clinically meaningful reductions in glycemic parameters over 24 weeks. At baseline, HbA1c and FPG values were well balanced between groups, confirming successful randomization and eliminating concerns about baseline bias. By Week 24, both groups showed substantial decreases in HbA1c (mean reductions of approximately -0.78% for Test and -0.85% for Control) and FPG (mean reductions of approximately -1.4 mg/dL for Test and -2.0 mg/dL for Control). These changes were consistently negative, as expected in effective glucose-lowering therapy, and the distributions overlapped substantially, indicating similar efficacy profiles.

The ANCOVA analysis, adjusting for baseline values, confirmed that the least-squares mean differences between Test and Control were small (around -0.07% for HbA1c), with 95% confidence intervals that were narrow and entirely within the prespecified non-inferiority margins (0.4% for HbA1c) importantly; the non-inferiority criteria were clearly met. This means that the Test treatment is not clinically worse than the Control treatment by more than the accepted margin, and therefore can be considered a viable alternative.

Taken together, the descriptive statistics highlight the consistency and magnitude of glycemic improvement, while the ANCOVA results provide formal statistical confirmation of non-inferiority. The combination of balanced baseline values, meaningful reductions at Week 24, and adjusted analyses showing differences well within non-inferiority thresholds provides robust evidence that the Test treatment is non-inferior to the Control treatment in reducing HbA1c and FPG.

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