Optimal Analysis Approach For TRIFERIC Clinical Trial

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1 Executive Summary

This project's purpose is to provide an analysis approach that optimally partitions, explains, and models data from the TRIFERIC clinical trial. As part of the study's design, 103 patients on the UVA dialysis system were observed before and after the administration of TRIFERIC to see how various lab measurements, most significantly the amount of intravenous iron, changed. Furthermore, there were three consulting questions addressed in this report. In response to question 1, his visual analysis was insufficient to conclude that TRIFERIC did not work in the population. A longitudinal data analysis using intravenous iron dosage as the response should also be performed because the visual analysis was insufficient. In response to question 2, you cannot simply look at the endpoints for the analysis. In response to question 3, covariates need to be controlled for in the analysis.

2 Introduction

2.1 General Background

Over 650,000 people are affected by End-Stage Renal Disease (ESRD), the final and most severe stage of chronic kidney disease. Individuals are diagnosed with ESRD when their kidneys' ability to remove toxins from the blood falls below 15%. Dialysis and kidney transplant are the two available treatments at the moment. The latter option is significantly more difficult to achieve, so the majority of ESRD patients are on dialysis. Due to the impaired release of erythropoietin, a hormone that stimulates the production of red blood cells, from dysfunctional kidneys, ESRD patients usually experience ESRD-induced anemia, resulting in a low red blood cell count. Patients with ESRD need to receive erythropoiesis

stimulating agents (ESAs) to treat ESRD-induced anemia. ESAs are the main class of drugs used to regulate red blood cell levels to a certain target level. Patient responses to ESAs are highly diverse, and whether the patient has enough iron in the body to make new red blood cells is a crucial component in ESA effectiveness. The current standard for administering iron doses is via intravenous supplementation, but through the dialysate is also an option. TRIFERIC, the first and only FDA-approved treatment intended for the replacement of iron to maintain hemoglobin in adult patients with hemodialysis-dependent chronic kidney disease, is a potential substitute for intravenous iron supplementation. Although TRIFERIC is a more affordable option, it has not yet been proven to be effective on the 103 patients using the UVA dialysis system. Dr. Lobo possesses TRIFERIC clinical trial data and wishes to know how to conduct a more sensitive and powerful analysis.

2.2 Objectives

The main objective of this consultation is to provide an analysis approach that best partitions, explains, and models the data from the TRIFERIC clinical trial. Dr. Lobo also has three questions, which I address in this report:

1. Is his visual analysis enough to say TRIFERIC did not work in the population, and if not, what formal analysis should be carried out?

2. Can you simply look at the endpoints (January data versus August data) for the analysis?

3. What things need to be controlled for in the analysis?

3 Analysis Approach

3.1 Proposed Analysis

To determine the efficacy of the treatment, I suggest performing a longitudinal data analysis with intravenous iron dosage as the response, utilizing the TRIFERIC clinical trial data. A longitudinal data analysis appears to be the ideal option for a formal analysis for two reasons: 1) the study's focus is on observing changes in the response over time as a result of the predictors, and 2) the data was gathered by repeatedly assessing the same patients over time, specifically over an eight-month period. A longitudinal data analysis would more correctly model the change in response over time while accounting for confounding variables

by their inclusion in the model. Since the assumption of independent observations is violated, a longitudinal data analysis is preferable to a traditional regression analysis when dealing with longitudinal data, the kind Dr. Lobo possesses. The assumption is violated because repeated measurements from the same subject are inherently correlated with each other. For a regression analysis to produce reliable results and interpretations, this assumption is required. To take within-subject correlation into consideration, a longitudinal data analysis incorporates a covariance structure with non-zero off-diagonal elements, bypassing the assumption violation.

Fixed effects models and mixed effects models, which incorporate both fixed effects and random effects, are two models utilized in longitudinal data analysis. In fixed effects models, it is assumed that the relationship between the predictors and the response is fixed or consistent throughout all observations. Furthermore, all of the predictors used to train the model have fixed levels, or categories, resulting in the response being dependent on the effect of one of these fixed levels for each predictor. Mixed models, on the other hand, assume predictors have varying relationships with the response within groups but share the same fixed relationship across groups. A mixed effects model, as opposed to a fixed effects model, would be more appropriate, in my opinion. It is reasonable to infer that patient differences may have some influence on the response since some predictors in the data fluctuate randomly depending on the individual, which justifies the use of a mixed effects model. For instance, if red blood cell production is lower than normal, if there are other co-morbidities present, or if there is insufficient iron to create red blood cells, the patient's response to ESAs will be highly variable. Therefore, the required iron dosage varies from patient to patient, adding a random element.

In addition to the mixed effects model, implementing a linear spline with a time knot would be appropriate. The transition to TRIFERIC occurs between the third and fourth month, so the initiation of TRIFERIC is the ideal location for a time knot. If TRIFERIC is expected to have fewer patients on intravenous iron supplementation or a lower average daily intravenous iron intake, it can be inferred that the response will not be constant after TRIFERIC is initiated. As a result, a time knot will show the change in the response trajectory post-initiation of the treatment, and the time-knot coefficient can be utilized to draw inferences about TRIFERIC's effects.

3.2 Suggestions for Data Modifications

Before conducting the analysis, there are changes I advise making to the data and visual analyses in order to get better results and conclusions.

First, include a predictor that specifies the quantity of iron received as opposed to a binary predictor of whether it was received or not. Using a binary predictor in which the amount of iron received varies depending on the patient can result in biased results. Additionally, if data on the amount of iron received is available, include a predictor that indicates the change in the amount of iron received. Focusing on the change in iron received is more indicative of how an individual is responding to TRIFERIC. Having only the amount of iron received is less beneficial than the change in the amount of iron received since, as was already established, the recommended iron dosage changes from patient to patient.

Second, consider using covariates as predictors in the data. If the covariates are not adequately accounted for, changes in the response, notably a decrease in the amount of intravenous iron needed, can be attributed to random variation in the covariates. The absence of desired results is presumably due to Dr. Lobo's analysis not adequately accounting for covariate variability. Demographic information (e.g., age, race, and gender), supplemental lab data (e.g., ESA dosage, hemoglobin level, and percent saturation), co-morbidities, prior hospital visits, and time since initially starting dialysis are examples of possible covariates that are not included in the data but should be properly considered. By incorporating these covariates into the model during longitudinal data analysis, these covariates are controlled for in the study.

Third, it is not advisable to censor data, and this censoring issue needs to be resolved before performing further analyses. Removing patients who have not finished the entire eight-month clinical trial reduces the sample size, which is undesirable for a multitude of reasons. Reducing the sample size reduces statistical power, increases the margin of error, prevent findings from being extrapolated to the population, and most importantly, make results from analyses invariably inconclusive. Furthermore, excluding individuals from clinical studies that aren't complete can skew the data, indicating that TRIFERIC was effective or, at the very least, didn't hurt the patients when, in reality, it may have killed them, preventing them from completing the trial. The patients could be sorted into groups based on how long they have been participating in the trial, rather than excluding those with unfinished clinical trials from the data. The number of completed months, predetermined ranges of completed months, or whether the patient finished the clinical trial in its entirety could all be used to sort groups.

However, if Dr. Lobo wishes to keep the censored data, he should utilize a likelihood-based approach because it is the most effective method for dealing with the problems that occur with censored data.

4 Comments on Visual Analyses

First, the current visual analyses Dr. Lobo presented during the consultation were insufficient to draw any conclusions regarding whether TRIFERIC was effective in the population. Using the average aggregates the patients and neglects the changes from individual patients. Considering patients have different health circumstances and characteristics, it is preferable to look at individual changes in the response rather than the average. Moreover, it is challenging to determine whether particular groups demonstrated a reduction in the amount of intravenous iron that was required due to the patient data being aggregated.

Second, looking at the endpoints of a visual analysis is insufficient. If TRIFERIC is to be used as a long-term treatment, we want to evaluate if it works over time, not just for an eight-month period. Thus, the trend is more important to focus on than the endpoints.

Third, regarding the fifth month in particular, I have a concern regarding Dr. Lobo's IV Iron plot that I believe he should look into. Except for the IV Iron boxplot, all of Dr. Lobo's other boxplots have a rectangular box for the fifth month that indicates the interquartile range. In fact, the interquartile range is present in every month for each of the other boxplots. I recommend investigating the reason why the interquartile range for this specific month is absent.

5 Conclusions

I believe the analysis and recommendations made were the best that could be done given that Dr. Lobo did not offer any data to examine or work with. In response to question 1, his visual analysis was insufficient to conclude that TRIFERIC did not work in the population. A longitudinal data analysis using intravenous iron dosage as the response should also be performed because the visual analysis was insufficient. In response to question 2, you cannot simply look at the endpoints for the analysis. In response to question 3, covariates need to be controlled for in the analysis. The proposed analysis method is a longitudinal data analysis that employs a mixed effects model and a linear spline with a time knot. Aside from that,

recommendations focused on altering the data, such as switching the binary predictor from whether iron was received to how much iron was received, adding a predictor that shows changes in iron received, including covariates in the model, and not censoring data. As a last remark, and let me preface by saying that this is not Dr. Lobo's fault, but even if a more powerful and sensitive analysis is carried out, the most that can be determined is that TRIFERIC is associated with the change in intravenous iron dosage, not the of cause it. Given that every patient received TRIFERIC between the third and fourth month, there is no control group. If there is no control group on which to base the results, a major change in response cannot be attributed exclusively to the treatment's efficacy. Moving forward, it is best to use data with a control group or communicate to researchers the necessity of a control group.