Analysis of Clinical Trial Data
STAT 5400

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December 6, 2010

Abstract

A clinical trial was conducted to assess the safety and efficacy of a new medication for the management of blood glucose in diabetes patients. Two treatments (drug and placebo) were administered to two different groups of diabetes patients for twelve weeks. Based on the design of the trial, we analyze whether *i)* treatment is associated with improved control of blood glucose levels over the twelve-week trial, and *ii)* whether drug treatment is associated with an improvement over and above that associated with placebo.

1 Introduction

A clinical trial was conducted to assess the safety and efficacy of a new medication for the management of diabetes using multi-center, randomized, placebo controlled, and parallel design. The primary objective was to discern the efficacy of drug treatment from placebo in improving long-term (several months) patient blood glucose control, as measured by glycated hemoglobin levels (HbA1c). Higher HbA1c is associated with increased risk for diabetes-related complications. Data on primary efficacy variable (HbA1c), secondary efficacy variable (Fasting Blood Glucose), and several safety variables were collected at week zero (pre-dose) and week twelve (post-dose).

Based on the design of the trial, we justify an analysis to determine whether *i)* treatment (drug or placebo) is associated with significantly improved blood glucose control as indicated by a change in HbA1c and/or Fasting Blood Glucose levels over the twelve-week trial, and *ii)* drug treatment is associated with significant improvement over and above that associated with placebo. The analysis comprises three steps:

1. Use baseline (pre-dose) measurements to validate randomization by comparing patients in the two treatment groups across all variables.

2. Detect for changes in HbA1c and Fasting Blood Glucose levels from pre-dose to post-dose within each treatment group.

3. Discern between the effects of drug treatment and placebo on changes in HbA1c and Fasting Blood Glucose levels over the course of the trial.

Employing the analysis described herein, we conclude that *i)* patients randomly administered either treatment experienced improved control of blood glucose levels as reflected by the twelve-week change in primary and secondary efficacy measures, and *ii)* patients administered drug treatment experienced an improvement over and above that associated with placebo. In the following sections we detail the methods employed to arrive at this conclusion, provide the theoretical justification and quantitative validation of model assumptions, and summarize the results of our analysis.

2 Methodology

2.1 Trial Design

Of primary interest is the effect of drug intervention on long-term blood glucose control in diabetes patients. Changes in blood glucose experienced by patients in the trial must be considered relative to the *inherent variation* in blood glucose levels observed in the population of all diabetes patients. Therefore, clinicians seek to quantify inherent variation for the purpose of qualifying treatment effects. Conducting the trial at three different centers is a means of *blocking* or separating inherent variation in blood glucose levels from *sytematic variation* introduced by "nuisance factors," or sources of variability that are not of primary interest. Such "nuisance" factors may be as subtle as the time of day treatment is administered and the behaviours of employees at the center. In theory, blocking controls for such systematic sources of variation; thus, isolating the "true" variation.

This clinical trial can be classified as a two-factor randomized block experiment (Table 1), where the factors and respective levels are:

a. Treatment (factor-of-interest)

  i. Placebo

  ii. Drug

b. Center (blocking factor)

  i. Center 1

  ii. Center 2

  iii. Center 3

For each patient, measurements are repeated (one at pre-dose and post-dose, respectively) so observations are dependent in time. The measure ΔHbA1c_i collapses data, taking advantage of the repeated measures structure to make data amenable to randomized block analysis (Table 1).

2.2 Analysis

With the specified trial design, we analyze the effect of drug intervention via a three-step approach.

	Pre-dose			Post-dose		
	Center 1	Center 2	Center 3	Center 1	Center 2	Center 3
Drug	$HbA1c_1$	$HbA1c_1$	$HbA1c_1$	$HbA1c_1$	$HbA1c_1$	$HbA1c_1$
	⋮	⋮	⋮	⋮	⋮	⋮
	$HbA1c_9$	$HbA1c_{10}$	$HbA1c_{10}$	$HbA1c_9$	$HbA1c_{10}$	$HbA1c_{10}$
Placebo	$HbA1c_1$	$HbA1c_1$	$HbA1c_1$	$HbA1c_1$	$HbA1c_1$	$HbA1c_1$
	⋮	⋮	⋮	⋮	⋮	⋮
	$HbA1c_9$	$HbA1c_{10}$	$HbA1c_{11}$	$HbA1c_9$	$HbA1c_{10}$	$HbA1c_{11}$

Table 1: Two-factor randomized block design of clinical trial. Note the repeated measures (over time) structure.

1. Use baseline (pre-dose) measurements to validate randomization by comparing patients in the two treatment groups across all variables.

   Validating the randomization assumption reasonably assures that patients in both treatment groups are selected from the same underlying population (diabetes patients); thus, facilitating comparison between groups. Therefore, we compare the two treatments groups using a t-test for two independent samples on all baseline measurements.

2. Detect for changes in HbA1c and Fasting Blood Glucose levels from pre-dose to post-dose within each treatment group.

   For each patient, we take the twelve-week change in efficacy variables as the primary and secondary response measures (Table 2). Using the twelve-week change takes advantage of the "automatic blocking" introduced when repeated measurements are taken on the same experimental unit (patient) over time. For each treatment group, we separately utilize a t-test for pairwise dependent observations to determine if treatment is associated with a significant improvement (over time) in blood glucose management.

3. Discern between the effects of drug treatment and placebo on changes in HbA1c and Fasting Blood Glucose levels.

   Only if significant changes are detected from pre-dose to post-dose, need we proceed to the question of whether drug is more effective than placebo in improving blood glucose management. Furthermore, if the randomization assumption is valid, we may address this question using simple techniques. Based on the results of steps 1 and 2, we use the two-sample