Understanding Intention to Treat Analysis and Per Protocol Analysis

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Abstract

Randomized control trials (RCT) are usually done to see treatment efficacy and safety profiles. It has two critical flaws, i.e., patient's non-compliance and loss of data concerning measuring outcomes and the solution to this problem is Intention to Treat analysis [1].

Introduction

While conducting clinical trials we come to know about the complexities of analyzing results. There is a lot of protocol violations seen, and as a result, we require some statistical principles to evaluate data and then comes the role of intention to treat analysis (ITT). In randomized controlled trials, ITT use is highly recommended [1-3].

Understanding ITT

It includes all the patients who are randomized in statistical analysis and usually these patients should be analyzed as per their allocated treatment group even if the patient has refused or discontinued their intervention.
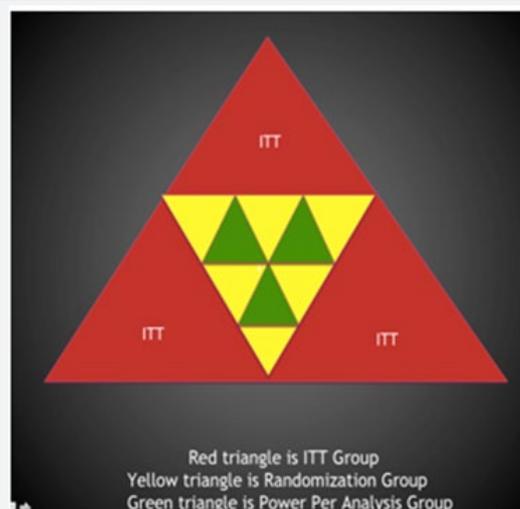
Figure 1: Depicts the total no of patients (n), i.e., Intention to treat in RCT shown as the red triangle and yellow triangle is patients who are randomized into standard treatment arm and test arm. The Green triangle represent that subset of ITT patients that are evaluated for Power per protocol analysis after patient exclusions from each arm depending upon various factors like withdrawn consent, lost to follow up, etc.

In head and neck cancer study author compared three weekly concurrent chemo radiation versus weekly concurrent Cisplatin. In this study total, 300 patients are randomized into arms of 150 each, but patients who completed treatment are 133 in three weekly arms and 141 in the weekly, but patients included in this trial for ITT are 150 in each division [3-5] (Figure 1).

Rationale of ITT

There is significant confusion in the understanding rationale that why we are including the patients in the analysis even if these patients have not received treatment regimen.

These patients are included in the analysis to maintain the rules of randomization because if self-selection excludes patients, then the benefits of randomization are lost as randomization is done to balance the factors in each arm that can introduce bias later on.

The second point of discussion is if we exclude non-adherent patients like in head and neck cancer study, 34 patients excluded from weekly Cisplatin and 18 from three weekly Cisplatin. This point will introduce the bias, and it can be concluded that patients who receive treatment have better outcome ignoring whether treatment is useful or not.

ITT has widespread use in clinical practice as it simulates the real clinical environment because in actual practice also patient doesn't often stick to the treatment depending on the various reasons.

ITT seems very attractive approach to deal with analysis, but there are also few issues associated with it. Suppose if inclusion criteria are not framed strictly and consequently at time of review there is a problem of excluding lot of patients and which in turn leads to violation of randomization.

The problem that we face with ITT is that it overestimates the effect of acceptance of non-compliance, dropping patients who do not adhere to treatment and protocol deviations. Patients who completed treatment as usual responded well and show the substantial effect of treatment. ITT is today standard for analysis in the clinical trial.

ITT preserves the sample size and hence protect the statistical power. It also minimizes type I error, and it is possible to generalize the results of RCT to the general population [5,6].

In contrary to above discussion Per Protocol analysis strictly adhered to the patients who stick to the treatment, so only those patients are analyzed who completed treatment. It gives the reliable estimation of effect between treatment and result. PPA is complicated to apply in clinical practice, and as per evidence, it is weak as compared to ITT. CONSORT (Consolidated Standards of reporting trials) guidelines strongly recommend providing the details of both estimates in clinical trials because when ITT and PPA come to the same conclusion, the confidence level in study results gets increased. There is modified ITT also available that will strictly deal with attrition and allow us to drop patient even after randomization like those patients who never started treatment after randomization. There are limitations to it that it is purely subjective and may allow users to manipulate data. There are no strict guidelines for application [7-10].

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