Intention-to-treat concept: A review

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Abstract

Randomized controlled trials often suffer from two major complications, i.e., noncompliance and missing outcomes. One potential solution to this problem is a statistical concept called intention-to-treat (ITT) analysis. ITT analysis includes every subject who is randomized according to randomized treatment assignment. It ignores noncompliance, protocol deviations, withdrawal, and anything that happens after randomization. ITT analysis maintains prognostic balance generated from the original random treatment allocation. In ITT analysis, estimate of treatment effect is generally conservative. A better application of the ITT approach is possible if complete outcome data are available for all randomized subjects. Per-protocol population is defined as a subset of the ITT population who completed the study without any major protocol violations.

Key words: Intention-to-treat analysis, per-protocol analysis, randomized controlled trials

INTRODUCTION

Randomized controlled trials (RCTs) often suffer from two major complications, i.e., noncompliance and missing outcomes. One potential solution to this problem is a statistical concept called intention-to-treat (ITT) concept. The objective of this article is to give a basic understanding of the ITT concept to the beginners in the field of clinical research. With this objective in mind, this article will review the ITT principle, with special emphasis on need and application of this concept and its pros and cons.

DEFINITION OF ITT CONCEPT

According to Fisher *et al.* (1990), the ITT analysis includes all randomized patients in the groups to which they were randomly assigned, regardless of their adherence with the entry criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol.[1]

In other words, ITT analysis includes every subject who is randomized according to randomized treatment assignment. It ignores noncompliance, protocol deviations, withdrawal, and anything that happens after randomization.[2-5] ITT analysis is usually described as "once randomized, always analyzed".[6,7]

ITT analysis avoids overoptimistic estimates of the efficacy of an intervention resulting from the removal of non-compliers by accepting that noncompliance and protocol deviations are likely to occur in actual clinical practice.[4]

NEED FOR SUCH A POPULATION

RCTs are the ideal design in assessing the efficacy and safety of medicine. In an RCT, the study subjects is randomly allocated to receive one of the treatments under study after assessment of eligibility but before the intervention is administered. Randomization in clinical trials reduces bias.

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The purpose of the RCT is to ensure that the groups differ only with respect to the interventions being compared.[8]

In an ideal scenario, every subject enrolled in RCT would follow instructions and complete their allocated treatment as described in the protocol and thus contribute data which were complete in all respects.[9] But unfortunately, one practical problem that investigators usually come across in RCT is that subjects do not always follow instructions. Moreover, in some studies, drop out of the subjects is a problem. Hence, RCTs often suffer from two major complications, i.e., noncompliance and missing outcomes. One potential solution to this problem is a statistical concept called ITT analysis.[10,11]

PROS OF USING ITT ANALYSIS

ITT is better regarded as a complete trial strategy for design, conduct and analysis rather than as an approach to analysis alone.[9,12] Full reporting of any deviations from random allocation and missing response is essential in the assessment of the necessity and appropriateness of an ITT approach, as emphasized in the Consolidated Standards of Reporting Trials (CONSORT) guidelines on the reporting of RCTs.[12] The CONSORT statement for improving the quality of reports of RCTs states that number of participants in each group should be analyzed by "intention-to-treat" principle.[13]

ITT analysis reflects the practical clinical scenario because it admits noncompliance and protocol deviations. ITT analysis maintains prognostic balance generated from the original random treatment allocation. It gives an unbiased estimate of treatment effect.[3,4,14] If noncompliant subjects and dropouts are excluded from the final analysis, it might create important prognostic differences among treatment groups. Moreover, subjects may be noncompliant or may drop out from the study due to their response of treatment.[3]

ITT analysis preserves the sample size because if noncompliant subjects and dropouts are excluded from the final analysis, it might significantly reduce the sample size, leading to reduced statistical power.[3]

ITT analysis limits inferences based on arbitrary or *ad hoc* subgroups of patients in the trial and emphasizes greater accountability for all patients enrolled in the study. Also, it minimizes type I error due to cautious approach and allows for the greatest generalizability.[15]

CONS OF USING ITT ANALYSIS

Many arguments against ITT analysis appear valid. To begin with, if a subject who actually did not receive any treatment is included as a subject who received treatment, then it indicates very little about the efficacy of the treatment. In ITT analysis, estimate of treatment effect is generally conservative because of dilution due to noncompliance. Also, heterogeneity might be introduced if noncompliants, dropouts and compliant subjects are mixed together in the final analysis. Moreover, end-point data will differ markedly among noncompliant, dropouts and compliant subjects, and interpretation might become difficult if a large proportion of participants cross over to opposite treatment arms.[3,4,12,16,17] ITT analysis has been criticized for being too cautious and thus being more susceptible to type II error.[12,15]

WHO SHOULD USE ITT?

A better application of the ITT approach is possible if complete outcome data are available for all randomized subjects. Care must always be taken to minimize missing responses and to continue to follow up those who withdraw from treatment.[4,18,19] Anyone who follows these principles intelligently and has a vision to minimize bias should not worry further about "intention to treat".[9] However, in most cases, missing data could also be dealt by using the last observation carried forward (LOCF) method, whereby the last available measurement for each individual at the time point prior to withdrawal from the study is retained in the analysis.[20,21]

US Food and Drug Administration (FDA) guidelines for "The Format and Content of the Clinical and Statistical Sections of Applications" state that as a general rule, even if the applicant's preferred analysis is based on a reduced subset of the patients with data, there should be an additional "intent-to-treat" analysis using all randomized patients. The FDA guideline further explains that the results of a clinical trial should be assessed not only for the subset of patients who completed the study, but also for the entire patient population randomized (the ITT analysis).[22,23]

Committee for Proprietary Medicinal Products (CPMP) note for guidance "Biostatistical Methodology in Clinical Trials for Marketing Authorisations for Medicinal Products" states that decisions concerning the analysis population should be guided by the principles underlying the "intention-to-treat" and the "per-protocol" strategies. When the ITT and per-protocol (PP) analyses come to essentially the same conclusions, confidence in the study results is increased.[22,24]

The International Conference on Harmonisation (ICH) E9 guideline on "Statistical Principles for Clinical Trials" uses the term "full analysis set" to describe the analysis set which is as complete as possible and as close as possible to the ITT ideal of including all randomized subjects.[22,25]

One of the alternatives of ITT analysis is the PP analysis. It is defined as a subset of the ITT population who completed the study without any major protocol violations.[26] PP analyses exclude all protocol violators, including anyone who did not adhere to treatment, switched groups, or missed measurements.[27] ITT tends to make the two treatments look similar, whereas the PP removes patients who do not complete treatment and is more able to reflect treatment differences.[28]

CPMP guideline states that for a superiority trial, the ITT analysis should be considered primary and the PP supportive.[29] It is often argued that the ITT analysis tends to dilute the treatment difference of interest.[30] Whereas the importance of the ITT population analysis in superiority designs has been well accepted, however there is no consensus about its role in non-inferiority trials.[31]

It has been argued that protocol violations and poorly conducted trials may cause the results obtained from two different treatment groups to appear similar. Hence, ITT analysis alone is not preferred for noninferiority trial. A possible alternative is to conduct the PP analysis where only subjects meeting the inclusion criteria are considered. But the conservative effect of the PP analysis on noninferiority and equivalence trials has not been thoroughly explored. Therefore, it has been suggested that noninferiority should be concluded only if both ITT and PP analyses permit that.[28,31-36] CPMP guideline states that in a noninferiority trial, the full analysis set based on the ITT principle and the PP analysis set have equal importance and their use should lead to similar conclusions for a robust interpretation.[29]

MODIFIED ITT CONCEPT

It is a subset of the ITT population and allows the exclusion of some randomized subjects in a justified way (such as patients who were deemed ineligible after randomization or certain patients who never started treatment). However, the definition given to the modified ITT (mITT) in randomized controlled trial has been found to be irregular and arbitrary because there is a lack of consistent guidelines for its application. The mITT analysis allows a subjective approach in entry criteria, which may lead to confusion, inaccurate results and bias.[27,37,38] It is mostly used in anti-infective trials where multiple mITT populations can be defined for a single study such as clinical mITT and microbiological mITT.[39,40]

SUMMARY AND CONCLUSION

One practical problem that investigators usually come across in RCT is that subjects do not always follow instructions. Moreover, in some studies, drop out of the subjects is a problem. Hence, RCT often suffers from two major complications, i.e., noncompliance and missing outcomes. One potential solution to this problem is a statistical concept called ITT analysis. ITT analysis includes every subject who is randomized according to randomized treatment assignment. It ignores noncompliance, protocol deviations, withdrawal, and anything that happens after randomization. ITT analysis is usually described as "once randomized, always analyzed". But in ITT analysis, estimate of treatment effect is generally conservative because of dilution due to noncompliance. Also, heterogeneity might be introduced if noncompliants, dropouts and compliant subjects are mixed together in the final analysis. Moreover, end-point data will differ markedly among noncompliant, dropouts and compliant subjects, and interpretation might become difficult if a large proportion of participants cross over to opposite treatment arms. A better application of the ITT approach is possible if complete outcome data are available for all randomized subjects. Care must always be taken to minimize missing responses and to continue to follow up those who withdraw from treatment. Anyone who follows these principles intelligently and has a vision to minimize bias should not worry further about "intention to treat".

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DISCLAIMER

The views and opinions expressed in this article are those of the author and do not necessarily reflect the official policy or position of his employer.

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