JAMA Guide to Statistics and Methods

The Intention-to-Treat Principle
How to Assess the True Effect of Choosing a Medical Treatment

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The intention-to-treat (ITT) principle is a cornerstone in the interpretation of randomized clinical trials (RCTs) conducted with the goal of influencing the selection of medical therapy for well-defined groups of patients. The ITT principle defines both the study population included in the primary efficacy analysis and how the outcomes are analyzed. Under ITT, study participants are analyzed as members of the treatment group to which they were randomized regardless of their adherence to, or whether they received, the intended treatment.[1-3] For example, in a trial in which patients are randomized to receive either treatment A or treatment B, a patient may be randomized to receive treatment A but erroneously receive treatment B, or never receive any treatment, or not adhere to treatment A. In all of these situations, the patient would be included in group A when comparing treatment outcomes using an ITT analysis. Eliminating study participants who were randomized but not treated or moving participants between treatment groups according to the treatment they received would violate the ITT principle.

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In this issue of *JAMA*, Robertson et al conducted an RCT using a factorial design to compare transfusion thresholds of 10 and 7 g/dL and administration of erythropoietin vs placebo in 895 patients with anemia and traumatic brain injury.[4] The primary outcome was the 6-month Glasgow Outcome Scale (GOS), dichotomized so a good or moderate score indicated success. The trial was conducted with high fidelity to the protocol so only a few patients did not receive the intended treatment strategy. Two patients randomized to the 7-g/dL study group were managed according to the 10-g/dL threshold and an additional 2 patients randomized to the 7-g/dL study group received one transfusion not according to protocol. The authors implemented the ITT principle and the outcomes for these 4 patients were included in the 7-g/dL group.

Use of the Method

Why Is ITT Analysis Used?

The effectiveness of a therapy is not simply determined by its pure biological effect but is also influenced by the physician's ability to administer, or the patient's ability to adhere to, the intended treatment. The true effect of selecting a treatment is a combination of biological effects, variations in compliance or adherence, and other patient characteristics that influence efficacy. Only by retaining all patients intended to receive a given treatment in their original treatment group can researchers and clinicians obtain an unbiased estimate of the effect of selecting one treatment over another.

Treatment adherence often depends on many patient and clinician factors that may not be anticipated or are impossible to measure and that influence response to treatment. For example, in the study by Robertson et al, some patients randomized to the higher transfusion threshold may not have received the intended therapeutic strategy due to adverse events associated with transfusion, fluid overload, or unwillingness of clinicians to adhere to the strategy for other reasons. These patients are likely to be fundamentally different from those who were actually treated using the 10-g/dL strategy. The characteristics that differ between patients who received the intended therapy and those who did not could easily influence whether a successful GOS score is achieved. If the ITT principle was not followed and patients were removed from their randomized group and either ignored or assigned to the other treatment group, the results of the analysis would be biased and no longer represent the effect of choosing one therapy over the other.

It is common to see alternative analyses proposed, eg, per-protocol or modified intent-to-treat (MITT) analyses.[5] A per-protocol analysis includes only study participants who completed the trial without any major deviations from the study protocol; this usually requires that they successfully receive and complete their assigned treatment(s), complete their study visits, and provide primary outcome data. The requirements to be included in the per-protocol analysis vary from study to study. While the definition of an MITT analysis also varies from study to study, the MITT approach deviates from the ITT approach by eliminating patients or reassigning patients to a study group other than the group to which they were randomized. Neither of these approaches satisfies the ITT principle and may lead to clinically misleading results. It has been observed that studies using MITT analysis are more likely to be positive than those following a strict ITT approach.[5] A comparison of results from ITT and per-protocol or MITT analyses may provide some indication of the potential effect of nonadherence on overall treatment effectiveness.

Noninferiority trials, which are designed to demonstrate that an experimental treatment is no worse than an established one, require special considerations with regard to the ITT principle.[6-8] Consider a noninferiority trial of 2 treatments— treatment A is a biologically ineffective experimental therapy and treatment B is a biologically effective standard therapy—with the goal to demonstrate that treatment A is noninferior to B. Patients may be randomized to receive treatment B, not adhere to the treatment, and fail treatment due to their nonadherence. If this happens frequently, treatment B will appear less efficacious. Thus, the intervention in group A may incorrectly appear noninferior to the intervention in group B, simply as a result of nonadherence rather than because of similar biological efficacy. In this case, the ITT

analysis is somewhat misleading because the noninferiority is a result of poor adherence. In a noninferiority trial, both ITT and per-protocol analyses should be conducted and reported. If the per-protocol results are similar to the ITT results, the claim of noninferiority is substantially strengthened.[6-8]

What Are the Limitations of ITT Analysis?

A characteristic of the ITT principle is that poor treatment adherence may result in lower estimates of treatment efficacy and a loss of study power. However, these estimates are clinically relevant because real-world effectiveness is limited by the ability of patients and clinicians to adhere to a treatment.

Because all patients must be analyzed under the ITT principle, it is essential that all patients be followed up and their primary outcomes determined. Patients who discontinue study treatments are often more likely to be lost to follow-up. Following the ITT principle will not eliminate bias associated with missing outcome data; steps must always be taken to keep missing data to a minimum and, when missing data are unavoidable, to use minimally biasing methods for adjusting for missing data (eg, multiple imputation).

Why Did the Authors Use ITT Analysis in This Particular Study?

Robertson et al[4] used an ITT analysis because it allowed the effectiveness of their therapeutic strategies to be evaluated without bias due to differences in adherence. Failure to follow the ITT principle could have led to greater scrutiny of the trial results, especially if adherence to the intended treatments had been poorer.

Caveats to Consider When Looking at Results Based on ITT Analysis

Although the ITT principle is important for estimating the efficacy of treatments, it should not be applied in the same way in assessing the safety (eg, medication adverse effects) of interventions. For example, it would not make sense to attribute an apparent adverse effect to an intended treatment when, in fact, the patient was never exposed to the experimental drug. For this reason, safety analyses are generally conducted according to the treatment actually received, even though this may not accurately estimate—and may well overestimate—the burden of adverse effects likely to be seen in clinical practice.

While determining the effect of choosing one treatment over another, or over no treatment at all, is a key goal of trials conducted late in the process of drug and device development, the goals of trials conducted earlier in development are generally focused on narrower questions such as biological efficacy and dose selection. In these cases, MITT and per-protocol analysis strategies have a greater role in guiding the design and conduct of subsequent clinical trials. For example, it would be unfortunate to falsely conclude, based on the ITT analysis of a phase 2 clinical trial, that a novel pharmaceutical agent is not effective when, in fact, the lack of efficacy stems from too high a dose and patients' inability to be adherent because of intolerable adverse effects. In that case, a lower dose may yield clinically important efficacy and a tolerable adverse effect profile. A per-protocol analysis may be helpful in such a case, allowing the detection of the beneficial effect in patients able to tolerate the new therapy.

ARTICLE INFORMATION

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