Intention to Treat

Necessary But Not Sufficient

Intention to treat (ITT) is the principle and practice of analyzing all experimental study participants as members of the assigned study condition, regardless of whether they received or adhered to the treatments. In this editorial, I will review reasons why ITT is necessary, in addition to how it can be problematic in gerontological research. Options for analysis and recommendations for designing and conducting research that adheres to the gold standard of ITT are discussed.

ADVANTAGES OF INTENTION TO TREAT

A principle I have followed in my research career and taught to my mentees is to conduct high-quality research with transparency and honesty. Non-adherence to a treatment protocol, inability to get staff to comply with a treatment or measurement procedure, and factors that interfere with treatment delivery or receipt all matter and should be disclosed in a forthright manner. Only reporting on those people who adhered to or completed treatment has been shown in multiple papers to bias and over-estimate the effectiveness of treatments (DeMets & Cook, 2019). ITT may better reflect the real world of clinical practice in which some people discontinue treatment or fail to follow treatment instructions. Discontinuation of treatment, it may be argued, is a consequence of treatment and should be reflected in the analyses. In the final analysis, all participants are included in their randomized groups, and outcome data continue to be collected for those who stop receiving the intervention. ITT tends to produce a conservative estimate of treatment effectiveness. Using ITT also makes the study less likely to be underpowered, because the planned sample size is more preserved.

PROBLEMS WITH INTENTION TO TREAT

A second principle I have followed when planning and conducting a randomized controlled trial (RCT) is, "Don't shoot yourself in the foot." It has been argued that ITT can do just that. By this I mean that ITT can underreport effectiveness to such a degree that we erroneously dismiss a treatment that may help older adults. If a subgroup never receives the treatment protocol, receives a very small dose, or has missing outcome data, the inclusion of these people in the treatment group can obscure rather than illuminate the treatment's true effectiveness. Researchers and methodologists have argued that it is illogical to include in the analysis people who did not receive any of the treatment, received only a small dose, received the alternative treatment, or did not provide outcome data (Polit & Gillespie, 2010). Older adults are often lost to follow up due to severe illness, death, transportation problems, or an inability to locate the participant.

Another issue is how to handle the common problem of missing data from those who did not complete the intervention. If data collection stops for these participants, the missing data can be handled by carrying the last observation forward, non-responder imputation, or by imputing missing data as a failure of treatment (Dossing et al., 2016). Imputing missing data as a treatment failure is the most conservative approach. Any method of imputation complicates the interpretation of results.

OPTIONS

Although it is unlikely that ITT will soon be replaced as the gold standard, alternatives have been proposed. The term *modified ITT* means different things in different studies, but generally allows the exclusion of some participants post-randomization. Examples include excluding people who were deemed ineligible after randomization or who never started the treatment. A per-protocol analysis is a comparison of groups that only includes those participants who completed the treatment allocated. If reported alone, per-protocol analysis and other alternatives to ITT may in-

troduce confounding biases, such as a selection bias, that random allocation was designed to prevent. But if the intention to treat and per-protocol analyses produce similar conclusions, confidence in the results is enhanced.

A meta-analysis of 72 RCTs of biological or targeted interventions for rheumatoid arthritis found that modified ITT approaches that excluded patients from the analysis post-randomization did not bias treatment effects, compared to classic ITT analyses populations (Dossing et al., 2016). A systematic review of 475 RCTs found ambiguous and varied descriptions of post-randomization exclusions in modified ITT reporting (Abraha & Montedori, 2010).

RECOMMENDATIONS

Retention of participants becomes exceedingly important when ITT is used. Multiple strategies to reduce attrition need to be in place. Eligibility criteria may need to consider excluding from the study people who may be difficult to retain. Incentives for continued participation that are not overly coercive should be considered. Try to minimize the time between obtaining consent and study allocation. Make contingency plans for locating people, as some participants may change addresses or phone numbers and be hard to locate for follow-up appointments.

Study methods, intervention design, and staff training all can impact the ability to adhere to ITT. My advice along these lines includes designing a study and intervention that are feasible and not overly burdensome. Report any deviations from random allocation and from the protocol, as recommended in the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Set as a high priority collecting data on people who discontinue the treatment. Train staff thoroughly because it is important to retention, protocol compliance, and quality measurement. Be explicit in reporting the details of the ITT analysis and any alternative approach used. Explain how missing data were managed.

CONCLUSION

The purpose of a RCT analysis is to determine an accurate estimate of the differences in outcomes between randomly allocated groups—not to determine a conservative estimate that is biased against the group that is allocated to the experimental intervention. No analysis option is perfect. Although it appears that ITT is here to stay, it is not without flaws and has the potential to misrepresent intervention efficacy. But ITT forces us to "up our game" when planning, conducting, and analyzing data from our research. Adhering to ITT and also reporting results of a per-protocol analysis meet both of my guiding principles of being honest and transparent while not sabotaging the reported findings because of forces that may be outside one's control.

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