Inclusion of patients in clinical trial analysis: the intention-to-treat principle

Stephane R Heritier, Val J Gebski and Anthony C Keech


determining the sample of participants to be analysed is a crucial step in reporting clinical trials. For such analyses, the gold standard is the “intention-to-treat” principle. The question of which participants are included in the analysis appears as Item 16 of the CONSORT statement (Box 1). 1

Intention-to-treat (ITT)

Analysis by ITT is a strategy that compares the study groups in terms of the treatment to which they were randomly allocated, irrespective of the treatment they actually received or other trial outcomes. Regardless of protocol deviations and participant compliance or withdrawal, analysis is performed according to the assigned treatment group. 2,3

Random allocation aims to ensure that trial participants’ risk factors that may affect the outcome under investigation are balanced between the allocated treatments. This is to ensure that any differences in outcomes observed between groups are actually a result of the trial interventions. Importantly, there can be no guarantee that participants from each group who do not comply with the allocated treatment have the same risk-factor profile. Any analysis other than an ITT analysis (eg, one that excludes non-compliant participants) will potentially compromise the balance of these factors and introduce bias into the treatment comparisons.

Thus, the ITT strategy generally gives a conservative estimate of the treatment effect compared with what would be expected if there was full compliance. By accepting that non-compliance and protocol deviations are likely to occur in actual clinical practice, 3,4 ITT essentially tests a treatment policy or strategy, and avoids overoptimistic estimates of the efficacy of an intervention resulting from the removal of non-compliers.

Ensuring ITT produces meaningful answers

The reality of conducting clinical trials means that the ITT principle is not usually fully met, especially when outcome data are missing for some participants. However, clinical trial researchers should consider this principle an ideal, and steps to achieve it should be considered in both the design and conduct of a trial.

Firstly, eligibility errors can be avoided by careful scrutiny before random allocation. Indeed, allocation of ineligible patients should be the exception, unless eligibility cannot be assessed quickly. Secondly, all efforts should be pursued to ensure minimal dropouts from treatment, crossover of participants between groups and losses to follow-up. An active run-in phase may be feasible to identify patients who are likely to drop out. A thorough consent process for participants and education of investigators will also minimise the
number of dropouts. During the trial, adequate warning of the potential side effects of treatment, together with ongoing clinical support and reassurance, should be available to all participants. When a proportion of participants are expected to receive a treatment different from the assigned one, a dilution effect generally results. The subsequent potential loss of study power can be accounted for by increasing the planned sample size. 5

Box 2 details the advantages and limitations of ITT analyses.

Alternatives to ITT analysis

Per-protocol (PP) analysis

There is a view that only patients who sufficiently complied with the trial’s protocol should be considered in the analysis. 6 Compliance covers exposure to treatment, availability of measurements, and absence of major protocol violations. Such an analysis is often referred to as a “per-protocol” or “on treatment” analysis. The main issue arising from this approach is that it might introduce bias related to excluding participants from analysis. Therefore, the ITT analysis should always be considered as the ideal primary analysis, possibly supplemented by a secondary analysis using the PP approach. However, if investigators decide differently, their choice must be justified and should be subject to strict rules. 7-9

Treatment-received (TR) analysis

Another approach is to analyse all participants according to the treatment they actually received, regardless of what treatment they were originally allocated. While this may have some initial appeal, once again the effect of random allocation is compromised, making the interpretation of the results difficult.

The impact of various approaches is illustrated in Box 3.

When ITT requirements are not fully met

A number of strategies can be adopted if the assumptions underpinning ITT are not satisfied.

If the crossover/non-compliance rates are small, then an ITT analysis should be the principal method of analysis. There is still some debate about whether ineligible subjects can legitimately be omitted from the final analysis. 2 For instance, in a study involving a potentially life-threatening condition, such as severe acute respiratory syndrome, treatment may be routinely commenced before laboratory confirmation of the diagnosis. If the patients subsequently are not diagnosed with the condition, there may be a case for excluding them from the ITT population. In these instances, a “modified” or “quasi” ITT population may be defined, allowing for such exclusions. The following principles should be followed to allow participants to be excluded from such an analysis:

- the criteria for exclusion from the analysis should be pre-specified in the protocol, be objective and clearly defined; 7,8 and,
- to remain unbiased, decisions to exclude participants need to be made (i) by researchers blinded to treatment allocation, and (ii) on the basis of information not related to either the allocated treatment or to events or outcomes that occur after random allocation.
In all circumstances, all patients randomly allocated to a study arm should be followed up, as exposure to study treatment may still influence their safety and place them at risk of serious adverse events. All efforts must be made to ensure maximum compliance and that patients continue to take their allocated treatments, and that all patients are accounted for in the trial report.9

The modified or quasi ITT population may also be useful when outcomes are not assessed in all participants. For example, outcomes requiring colonoscopic follow-up can result in no information for patients who, for any reason, did not undergo colonoscopy during the study, requiring an analysis based on a subset of the patient population.10 In such a case, modifying the ITT population allows some clinical interpretation of the results.

A more extreme example is a study evaluating hip protectors, in which only around 50% of those in the intervention arm were wearing a hip protector at the time of their fracture.11 In this situation, neither an ITT or per-protocol analysis would necessarily provide reliable information about the value of hip protectors when actually worn.

There has been debate about the appropriateness of imputing missing values.4 If missing data are imputed, it is recommended that some sensitivity analysis be performed to ensure that study conclusions are not misleading.4,12

Conclusion
ITT analysis gives unbiased and consistent estimates of a treatment policy, and should, wherever possible, be the analysis of choice. Deviations from this principle compromise the balance between groups that is achieved by random allocation, and are rarely justifiable as a principal analysis.

Competing interests
None identified.

References
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. 4. Heritier SR, Gebski VJ, Keech AC (2003) Inclusion of patients in clinical trial analysis: The intention-to-treat principle. Med J Aust 179(8): 438- 440. 5. Hollis S, Campbell F (1999) What is meant by intention to treat analysis. Survey of published randomized controlled trials. Intention to treat analyses are done to avoid the effects of crossover and dropout, which may break the random assignment to the treatment groups in a study. ITT analysis provides information about the potential effects of treatment policy rather than on the potential effects of specific treatment. To address some of these issues, many clinical trials have excluded participants after the random assignment in their analysis, which is often referred to as modified intention-to-treat analysis or mITT. Trials employing mITT have been linked to industry sponsorship and conflicts of interest by the authors.[4]. Inclusion of patients in clinical trial analysis: the intention-to-treat principle â€“ eMJA. Determining the sample of participants to be analysed is a crucial step in reporting clinical trials. For such analyses, the gold standard is the â€œintention-to-treatâ€ principle. The question of which participants are included in the analysis appears as Item 16 of the CONSORT statement (Box 1).1. The full article is accessible to AMA members and paid subscribers. Login to read more or purchase a subscription now.