Intention-to-treat analysis: Who is in? Who is out?

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KEY POINTS FOR CLINICIANS

- Including all randomized subjects when analyzing randomized controlled trials—the "intention-to-treat" principle—is an important factor in minimizing bias.
- Studies have found that fewer than half of randomized controlled trials reported intention-to-treat analysis.
- Among studies reporting intention-to-treat analyses, fewer than half actually analyzed all randomized subjects.

To assess whether the term "intention to treat" (ITT) predicts inclusion of all randomized subjects in the analysis, we reviewed 100 randomly selected reports of randomized trials that mentioned analysis by ITT. Only 42 of 100 reports included all randomized subjects in the ITT analysis. We could not determine which categories of participants were excluded from the ITT analysis in 13 trials. The most common categories of excluded subjects were patients who, after randomization, received no follow-up (16/100), received no treatment (14/100), or were found not to meet study entry criteria (12/100). We could determine the number of participants in the ITT analysis for 92 studies. Nineteen of the 92 studies excluded more than 5% of randomized participants, and 10 excluded more than 10%. There is considerable variation in how researchers define and apply the principle of intention to treat.

■ KEY WORDS Randomized controlled trials, research design, random allocation, intention to treat. (*J Fam Pract 2002; 51:969-971*)

The randomized controlled trial (RCT) has become the most important test of therapeutic benefit.[1] When evaluating an RCT, readers should determine whether the analysis was by intention to treat (ITT).[1–4] ITT analysis, often described as "once randomized, always analyzed,"[5] is the practice of attributing all participants to the group to which they were randomized, regardless of what subsequently occurred.[2,6,7] ITT analysis avoids the problems created by omitting dropouts and noncompliant patients, which can negate randomization, introduce bias, and overestimate clinical effectiveness.[2,8]

Surveys of the literature found that ITT analysis was reported in 7% to 48% of RCTs[8–10]; however, reporting ITT analysis does not guarantee that the analysis was conducted properly or that the results promoted by the authors were derived from the ITT analysis. For articles reporting ITT analysis of an RCT, we specifically examined which participants were included in the analysis.

METHODS

We searched MEDLINE for abstracts that included the text words "intention to treat" or "intent to treat," limiting the results to randomized controlled trials published in English during 1999. We entered the resultant studies in a database (FileMaker Pro 4.0; FileMaker, Inc., Santa Clara, CA), ordered them using the database's random number function, and reviewed the first 100 eligible studies.

Two of us (in a rotating fashion cycling through each pair-wise combination of the 6 authors) were systematically assigned to review each article. We used a structured form (available on request from the authors) to evaluate each article for the number of subjects randomized, the number in the ITT analysis, the number in the primary analysis, which categories of subjects were in the ITT analysis, and where ITT was defined within the article. We defined the primary analysis as the most prominently featured outcome in the abstract. Two of us (R.L.K., J.J.S.) independently assessed whether articles contained a diagram showing the flow of participants through each stage, a feature strongly recommended in the Consolidated Standards of Reporting Trials (CONSORT).[3] All coauthors discussed discrepant results and made final determinations using majority voting. We conducted all

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analyses using SAS software (SAS system for Windows, Release 8.0; SAS Institute, Cary, NC).

RESULTS

The MEDLINE search identified 335 studies. We reviewed 129 articles to obtain 100 eligible studies (Figure). We excluded articles for the following reasons: the words "intent" or "intention" and "treat" did not refer to a method of analysis (14); the study was not an RCT (5); the study involved randomized groups (eg, villages or hospitals) rather than individuals (4); the study presented a secondary analysis of a previously published study (4); the study used a crossover design (1) or described a trial protocol without results (1). The paired reviewers agreed on all abstracted data elements for 83 articles; there was a disagreement on one or more items for the remainder, which were determined by committee.

Of 100 studies selected, 42 included all randomized subjects in the ITT analysis (Table). Among those studies that excluded randomized patients from analysis, the most common reasons given were that the patients received no follow-up after randomization (16) or received none of the allocated treatment (14). For 13 studies, we could not determine which categories of participants were excluded from the ITT analysis.

We used the number of subjects randomized, the number in the ITT analysis, and the number in the primary analysis to determine the proportion of randomized subjects in both the ITT and primary analyses. Ideally, 100% of randomized subjects should be included in the ITT analysis. The proportion of randomized subjects included in the ITT analysis could be determined for 92 studies, and ranged from 69% to 100%, with a median of 99%. Nineteen of the 92 studies (21%) excluded more than 5% of randomized participants from the ITT analysis, while 10 studies (11%) excluded more than 10%.

We could determine the proportion of randomized participants in the primary analysis in 93 studies; it varied from 49% to 100%, with a median of 98.7%. Ten of the 93 studies (11%) excluded more than 20% of participants from the primary analysis. In 16 of the 93 studies (17%), a non-ITT analysis (eg, "per protocol") was presented as the primary analysis. In these studies, an average of 80.1% (median, 82.4%; range, 49.0% to 92.4%) of randomized patients were included in the primary analysis.

Fifty-six studies included a definition of the ITT population, primarily within the methods (38) and results (18) sections. Of the 42 studies where all randomized subjects were analyzed, 20 included definitions of ITT. Diagrams showing the flow of participants through each trial were present in 41 of 100 articles, including 1 on a journal's web site. An additional 8 articles had diagrams that showed patient flow without giving the number of patients. Presence of a flow diagram was not related to whether or not all randomized subjects were included in the ITT analysis (36% vs 45% respectively, $P = .37$). Of the 31 articles from journals that participate in CONSORT, 29 included flow diagrams, compared with 12 of the 69 articles from journals that do not participate in CONSORT ($P < .0001$).

DISCUSSION

The hallmark of ITT analysis is that all randomized subjects are analyzed.[7] In more than half of the articles we examined, this was not the case. Analysis of only certain subgroups of patients is sometimes appropriate, but an explanation should be provided whenever subjects are left out of any analysis. For example, we examined a report of a trial that was stopped based on the results of an interim analysis, thus excluding subjects who were randomized after the interim analysis.[11] This type of exclusion, based on an a priori decision rather than individual characteristics or behavior, is less likely to bias results.

While all the articles in our sample reported analysis by ITT, many authors did not define the term, even when they excluded some randomized subjects from the ITT analysis. In these cases, the reader is left to infer which subjects were excluded based on information given in the text, figures, and tables.

Despite numerous recommendations for detailed reporting of RCT methods,[1–4] many articles were vague and lacked detail. We could not determine which categories of participants were excluded from the ITT analysis in 13 articles. In 8 of the

TABLE

Categories of randomized patients excluded from ITT analysis*

Category	Number of studies
All randomized subjects were analyzed (true intention to treat)	42
Some randomized subjects were excluded	58
Subjects found not to meet entry criteria	12
Subjects who did not receive any of the assigned treatment	14
Subjects who received some but not all of the assigned treatment	1
Subjects with no follow-up after randomization	16
Subjects with some but not all follow-up achieved	1
Subjects who dropped out for selected reasons	4
Subjects with specific protocol violations	2
Subjects with protocol violations but details not given	2
Other	9
Author needs to be contacted to determine who was in the ITT group	13

*Reports of 100 randomized trials were analyzed. Studies could have more than one group of excluded subjects.
ITT, intention to treat.

100 articles we examined, we could not determine how many subjects were randomized or included in the ITT or primary analysis. Four of these 8 articles were in journals that endorsed the CONSORT statement. All were published well after the initial CONSORT statement was released in 1996.[1]

The number of randomized subjects excluded from the ITT analysis was usually small. It is unlikely that excluding up to 1% of subjects had a major effect on the results. In 11% of our sample, however, more than 10% of randomized subjects were excluded. Exclusions of this magnitude have significant potential to alter the findings. When outcome data can't be determined and the outcome is categorical (eg, alive/dead), it can be helpful to produce best-case and worst-case scenarios in which patients lost to follow-up are arbitrarily ascribed good or bad outcomes. These extremes delimit the potential effect of the exclusions on results.[12] Similarly, missing continuous outcomes (eg, weight change) can be assigned specific values to determine the potential impact on the results.

We assessed only articles that mentioned ITT in the abstract, so we probably missed some studies that used ITT analysis; however, we doubt that this caused us to significantly underestimate accurate use of the term ITT. The articles came from a wide spectrum of journals (62), of which 21 were listed in the *Abridged Index Medicus* subset. The 17 articles requiring a committee vote described the analytic process in terms that were often vague and ambiguous. In these cases, we cannot be certain that we correctly interpreted the authors' methods; most readers would have similar difficulties.

We found considerable variation in how the term ITT was used in reports of RCTs. Fewer than half of the reports we examined included all randomized subjects in the ITT analysis. While exclusions were negligible in many cases, more than 10% of the subjects were excluded in 10% of the trials. In 7 trials, including some drawn from journals that endorse the CONSORT statement, it was not even possible to determine the number of subjects included in the ITT analysis. These problems highlight the continued need for better reporting of clinical trials.

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