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

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1: CONSORT checklist of items to include when reporting a trial

Selection and topic	Item no.	Descriptor
Numbers analysed	16	Number of participants (denominator) in each group included in each analysis, and whether the analysis was by "intention to treat". State results in absolute numbers (eg, 10/20, not 50%).

2: Advantages and limitations of an intention-to-treat (ITT) analysis

Advantages

- Retains balance in prognostic factors arising from the original random treatment allocation
- Gives an unbiased estimate of treatment effect
- Admits non-compliance and protocol deviations, thus reflecting a real clinical situation

Limitations

- Estimate of treatment effect is generally conservative because of dilution due to non-compliance
- In equivalence trials (attempting to prove that two treatments do not differ by more than a certain amount), this analysis will favour equality of treatments
- Interpretation becomes difficult if a large proportion of participants cross over to opposite treatment arms

Requirements for an ideal ITT analysis

- Full compliance with randomised treatment
- No missing responses
- Follow-up on all participants

ITT analysis is highly desirable unless:

- there is overwhelming justification for a different analysis policy (eg, an unacceptably high proportion of ineligible participants — those without the disease under study, for whom there is no potential benefit from the intervention. In these circumstances a "quasi" ITT approach (in which ineligible patients are excluded) is more appropriate.

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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

3: Example illustrating the impact of intention-to-treat, per-protocol and treatment-received analyses in a placebo-controlled trial*

	Treatment group (n=1000)		Control group (n=1000)		
	Compliers	Non-compliers (drop-outs)	Compliers	Non-compliers (drop-ins)‡	
Compliance 80%†‡	800†	200†	800‡	200‡	
Untreated baseline risk	10%	10%	7.5%	20%	
Number of events without any treatment	80	20	60	40	
Overall event rate	100/1000 = 10%		100/1000 = 10%		
Expected number of events					**Expected benefit (relative risk reduction)**
Full compliance	80		100		20% benefit (1 – [80/100])
Intention-to-treat analysis	64	20	60	32	9% benefit (1 – [84/92])
Per-protocol analysis	64	—	60	—	7% detriment (1 – [64/60])
Treatment-received analysis	80	20	60	32	40% detriment (1 – [112/80]§)

Trial assumptions

* The average risk of each group is 10% over the long term trial duration, and active treatment, when taken, reduces the risk by 20%.

† 20% of those allocated to receive the active drug do not take it because of early side-effects unrelated to the study outcome.

‡ 20% of those allocated to receive the matching placebo medication are prescribed the active therapy because of early clinical deterioration of their condition directly related to their risk of study outcome (these participants are a high-risk subset and have double the average risk [ie, 20%]).

§ This comprises expected events in those taking the active drug (treatment group compliers and control group non-compliers) divided by those not taking the active drug (control group compliers and treatment group non-compliers).

A simple adjustment factor to obtain a better estimate of what might happen with full compliance (100%) compared with observed compliance (80% for each group) can be applied to the ITT benefit (ie, 9% x 100/80 x 100/80 = 13% benefit).

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.

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book review

Integrating complementary therapies

Integrative medicine. David Rakel. Philadelphia: Saunders, 2003 (xxi + 821 pp, $163.90). ISBN 0 7216 9288 5.

THIS EDITED COLLECTION is an ambitious attempt to provide an evidence-based overview of integrative medicine. In addition to presenting the most appropriate complementary, alternative and conventional therapies for a range of conditions, a long list of US-based medical authors also provide an overview of the philosophy of integrative medicine and a guide to the practical techniques which underpin an integrative approach.

Doctors today are expected to have an understanding of complementary therapies to facilitate discussions with patients, so this book is timely. The scope of the work is extremely broad and is mostly successful. The philosophy section is kept very brief and sets the stage for the therapeutic chapters without going into detail about specific modalities. The therapeutic chapters provide a somewhat random account of different medical conditions, along with a review of suitable therapies. While evidence is provided to support the text, the information is more practical than academic and is aimed at clinicians or students rather than researchers. The therapeutic review section at the end of each chapter presents a list of options without prioritising or providing specific treatment protocols.

The final sections of the book provide information on disease prevention as well as a "tools for your practice" section, which provides a user guide to interventions that can be used to complement conventional treatments. This section presents an overview of interventions such as diet, antioxidants, meditation and exercise, but does not provide enough information to offer detailed instruction or to be prescriptive.

At around $160, the book is a relatively expensive addition to the library, yet it does provide a practical and comprehensive, if somewhat superficial and US-centric, overview. It also provides an excellent starting point for discussing complementary treatments with patients or integrating a wider range of therapies into mainstream practice.

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intention-to-treat principle. 4. trial analysis. 4. clinical trial. 4. inclusion patients. 4. patients clinical. 4. principle. 1. inclusion.Â Follow us on Twitter to stay on top of the latest in scientific research. Press proceed to send the authors a message. Follow PubFacts. Proceed.