

## EVIDENCE BASED MEDICINE

# Clinical Applicability of Intention-to-Treat Analyses

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### ABSTRACT

Interpreting the results of a clinical trial requires critical appraisal of the methodology. The reader should analyze the statistical reporting method employed, whether it is “intention-to-treat” or “method-effectiveness” models. This article reviews the advantages and disadvantages of the intention-to-treat method of statistical reporting and provides an example of where its use can dramatically alter a trial’s apparent results. It concludes that it is crucial for clinicians to be aware of the reporting model employed and that applicability to individual patients must always be of primary importance.

### INTRODUCTION

The randomized controlled trial (RCT) is the gold standard for comparison between two or more treatment options. There are several factors that contribute to high-quality RCTs. These include, but are not limited to: un-biased randomization protocols, appropriate levels of blinding and optimal patient follow-up. Another factor that is less commonly addressed is the method of statistical analysis, despite the fact that it may completely alter the perceived results of a trial.

In this article, the authors will examine one aspect of the statistical reporting of clinical trials: how researchers should deal with participants who do not adhere to the treatment to which they were randomized. In particular, we will explore the utility of the “intention-to-treat” analysis, and discuss the advantages and disadvantages of this model in comparison with alternative models.

### INTENTION-TO-TREAT: THE ESSENTIALS

Ideally, all patients in a clinical trial receive the treatment to which they are randomized. Despite the best efforts of clinical investigators, however, a number of patients in many studies will deviate from the plan and decide to either switch treatment regimens or receive no treatment at all.

Two questions arise when such non-adherence occurs. First, did the underlying prognosis differ in those patients in whom treatment was discontinued or switched versus

patients who complied with their assigned treatment? For example, if a participant becomes too sick to attend regular follow-up, they may discontinue participation or opt for a more aggressive therapy.

The second question that a case of non-adherence poses is whether the reason for non-adherence is related to the therapy itself. For example, was the therapeutic regimen too demanding, were the side-effects intolerable, or was the prospect of a surgical intervention too frightening for the participant? If patients who are non-adherent differ in prognosis, and the reasons for non-adherence differ in intervention and control groups, the prognostic balance created by the original randomization is liable to be undermined by excluding non-compliers.

Keeping these two questions in mind, trial investigators must decide how to report patients’ outcomes in such cases: Should patients who do not complete the treatment be analyzed in the groups to which they were originally randomized, or should they be excluded from the statistical analysis altogether (a so-called “per-protocol” analysis)? And, if patients have opted to receive treatment from another arm of the study, should they be analyzed as part of that group instead (a so-called “as-treated” analysis)?

In two recent reviews of published RCTs, approximately one-half of trial investigators were found to have dealt with the above situation by employing an intention-to-treat analysis.<sup>1,2</sup> This method, sometimes referred to as “once ran-

domized, always analyzed”,<sup>1</sup> involves assigning non-adherent patients’ outcomes to the arm of the study to which they were randomized, despite the treatment they may have actually received. Some proponents of this analytical technique believe that the answers to the two questions are most likely affirmative, in that patients’ prognoses differ in compliers and non-compliers and that the reasons for non-compliance are indeed likely to differ in intervention and control groups. If this is so, then analyzing patients in the groups to which they are randomized is the only way to preserve the prognostic balance of the original randomisation and limit the potential biases created by differences in baseline participant prognoses.<sup>3-5</sup>

If a participant’s poor prognosis is related to their non-adherence, excluding them from analysis will result in an apparent increase in the “health” of those in the arm to which the patient was randomized, and may thus inflate the benefit of the therapy. Intention-to-treat analyses limit such biases.

In addition, some view the intention-to-treat approach to be the most realistic way to view a treatment regimen, in that it captures the real-life prospect that patients do not (or cannot) always adhere to a planned program. In this way, the intention-to-treat method is proposed to be a valid measure of the true effectiveness of a treatment plan, as opposed to the biological efficacy of a treatment itself.

### ALTERNATIVES TO INTENTION-TO-TREAT

Although “intention-to-treat” appears to be the most employed method when dealing with the question of subject non-adherence, it is not without its disadvantages, the largest of which may be that it may provide an excessively conservative estimate of the magnitude of treatment effect. The randomized controlled trial assumes that the outcomes observed will be more or less equivalent in patients in clinical trials as in patients in actual clinical scenarios. A clinician’s reliance on the intention-to-treat principle further assumes that the reasons for which a study participant elects to deviate from a prescribed treatment are the same as the reasons for which a patient would deviate in a real clinical scenario. Some authors have pointed to flaws in this assumption and believe that the reasons for non-adherence in clinical trials could be far different than those in real life. For example, patients in clinical trials are subject to greater scrutiny and are more informed, and may thus be more prone to re-assess the status of their therapy.<sup>6</sup> Moreover, patients in clinical trials give consent to two or more possible treatment regimens before randomization. These patients may therefore have more reason to reconsider their treatment than a patient who sits with his or her physician and makes an informed choice to proceed with a single treatment regimen.

Alternatives to the intention-to-treat method exist and are categorized as “method-effectiveness” models. The most popular among them include the “per-protocol” method (in

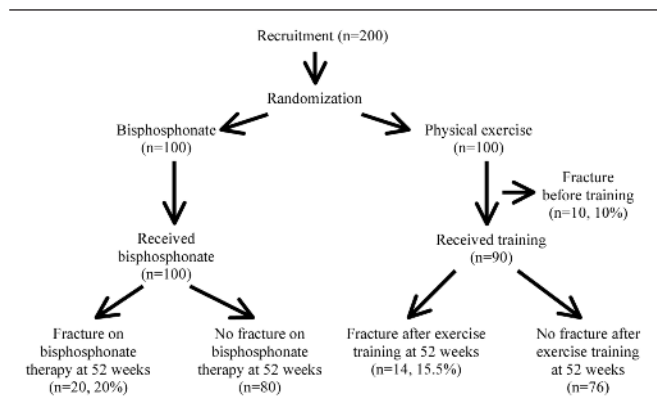
which only patients who adhere to their assigned therapeutic plan are included in statistical analysis) and the “treatment-received” or “as-treated” method (in which patients who switch between arms of the trial are included in the statistics of the arm in which they finished the trial).<sup>3,6</sup>

The abovementioned alternatives to the intention-to-treat method may be practical where evidence-based medicine and individual patient care converge. For instance, an inspired patient may wish to know how a proposed therapy could benefit them, and not how it works in a large group of individuals with varying levels of interest or motivation. A clinical trial that has employed the intention-to-treat method is not likely to provide this information, unless it has demonstrated a very low rate of patient non-adherence or the rate of non-adherence (for practical reasons) reflects the probable ability of an individual patient to complete the prescribed therapy.

### INTENTION-TO-TREAT EXEMPLIFIED

Consider a hypothetical clinical trial which compares the benefits of two therapeutic regimens: medical therapy with a bisphosphonate versus training in weight-bearing physical exercise in 200 high-risk elderly women as preventative therapies for hip fractures (Figure 1). Suppose that those assigned to the physical exercise training regimen experience a six-week delay from the time of randomization to the time they actually receive their training, and that 10% of participants in this arm experience a fracture during the first six weeks. In the group who actually completed exercise training there are 14 participants who go on to experience fracture after one year, and in the bisphosphonate arm a total of 20 participants fracture over one year.

Using an intention-to-treat model, which would include the women who fractured in the first six weeks without receiving physical training, the bisphosphonate arm would be reported to experience a 20% fracture risk (20/100 subjects) and the physical training arm a 24% fracture risk (24/100 subjects). The bisphosphonate therapy would thus be a superior therapy. If, however, the ten patients who frac-



**Figure 1.** Sample randomised clinical trial.

tured in the physical training arm who had not yet received training were excluded from the analysis (i.e., in a “per-protocol” or “treatment-received” method), the fracture risk in the physical training arm would be reduced to 15.5% (14/90 subjects). Excluding those ten fractured but untrained women from the analysis would therefore inflate the apparent benefit of the physical training regimen and conclude that it was superior therapy.

As a clinician, the utility of the reporting system employed in the above example will depend on your own patient’s clinical situation. For example, if your patients generally experience wait-times for physical training similar to that described in the hypothetical trial, the intention-to-treat analysis would provide a practical and realistic conclusion. If, however, you have timely access to physical training for your patients, a “method-effectiveness” model would more appropriately generalize to your situation as your patients could immediately expect to experience the observed “treatment-received” benefit of the exercise regimen.

## CONCLUSION

The intention-to-treat analytical method has been reported by some to represent the gold standard of statistical reporting in clinical trials, and is described as the least biased method of interpreting trial results when non-adherence occurs.<sup>3,4,8</sup> Critics claim its use denies that clinical trial patients have a unique experience with regards to their treatments and that the reasons for their non-adherence may be related to trial participation.<sup>6</sup> The argument between “intention-to-treat” and “method-effectiveness” models essentially epitomizes the debate between the values of

knowledge of clinical effectiveness (i.e., utility in the real clinical situations) and clinical efficacy (i.e., utility in ideal situations). Many argue that the former is more important to ensure generalizability, and support the intention-to-treat method.<sup>5,7</sup> In either case, the ideal clinical trial is one in which non-adherence levels are low, which makes the differences between the analytical methods less significant. From the perspective of the clinician attempting to extrapolate clinical trial results to his or her patient, it is more important to understand and recognize which reporting method is being used rather than to presume that any study lacking an intention-to-treat method is wholly flawed. In conclusion, knowledge of the reasons for non-adherence in trial patients must be compared to the circumstances surrounding one’s own patients in order to determine the value of one model over another. Understanding the implications of using the analytical methods described in this paper will put clinicians in a better position to make sound evidence-based clinical decisions. †

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