

TOPICS IN TRAINING

THE INTENTION-TO-TREAT PRINCIPLE: A PRIMER FOR THE ORTHOPAEDIC SURGEON

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Randomization in clinical trials reduces bias. Its intent is to generate groups of patients that are comparable with each other before starting a study. As a result, both known and unknown patient factors that may affect the outcome under investigation are balanced between the treatment groups, minimizing the risk of differences between the two groups at the onset of the trial. This helps to ensure that differences in outcomes observed between the groups are the result of the intervention. Anything that compromises the balance of these factors may introduce bias into the results^{1,2}. If an imbalance between the groups skews the results in favor of one intervention over the other, this can lead to a biased study. Therefore, a randomized, double-blinded, placebo-controlled (when appropriate) trial with intention-to-treat analysis is considered to be the highest level of evidence in clinical research. This provides the clearest insight into the effect of the intervention being studied by controlling for as many factors as possible.

Intention-to-treat analysis compares study groups in terms of the treatment to which they were randomly allocated, irrespective of the treatment they actually received²⁻⁴. If subjects do not receive the treatment to which they were originally randomized, they are in violation of the study protocol. There are several examples of protocol violation, including crossover from one treatment group to another, patients lost to follow-up, and inclusion of patients who should not have been included. Regardless of protocol violation, intention-to-

treat analysis is done according to the originally assigned treatment groups because this helps to preserve the value of randomization.

Some investigators exclude from analysis any participants who violate the study protocol (e.g., those who cross over, are lost to follow-up, or have insufficient follow-up). This is known as per-protocol analysis³. Patients who deviate from the protocol are eliminated, and there is no guarantee that the residual groups are comparable⁵. The remaining treatment groups may be unbalanced in their initial patient factors. This undermines the reason for randomization and may introduce bias⁵. By excluding nonadherent participants from the analysis, those who may be destined to have a better outcome are left behind¹. This may overstate treatment efficacy. As such, per-protocol analysis should be considered a “best-case scenario.”

Let us illustrate these principles with a hypothetical example. Imagine a randomized trial in which treatment with a cast is compared with intramedullary nailing for low-energy fractures of the tibia. Assume that both treatments are equivalent. Fifty patients are enrolled, with twenty-five randomized to each arm of the study (Fig. 1). The primary end point of the trial is the number of patients returning to a pre-injury level of function. Ten of the fifty patients are unmotivated and are destined for a poor outcome regardless of treatment assignment. In real life, patient motivation is not easily measurable, but randomization equally dis-

tributes immeasurable patient factors just as it does measurable traits. In our example, randomization equally distributes the unmotivated patients between the two groups (five in each treatment arm). All of the patients in the intramedullary nail group have uneventful surgery. All twenty-five patients in the other group have a cast applied, but five return for the one-week follow-up visit and want intramedullary nailing. Three of these five patients are unmotivated. At the end of the trial, all of the unmotivated patients have functional limitations regardless of the treatment they received.

With use of the per-protocol method of analysis, the five patients who cross over are excluded from analysis. The remaining groups are now no longer balanced, with more unmotivated patients in the intramedullary nail group. This leaves twenty patients in the cast group and the original twenty-five patients in the intramedullary nail group for consideration. Two (10%) of the twenty patients in the cast group and five (20%) of the twenty-five patients in the intramedullary nail group are unmotivated and have functional limitations. Therefore, it appears as if cast treatment is superior. In reality, the unmotivated patients will all do poorly regardless of the treatment they receive⁴. The per-protocol method systematically excludes the unmotivated patients from the cast group and introduces bias. With the application of the intention-to-treat principle, the patients who cross over are analyzed in the group to which they were originally randomized. As such, the

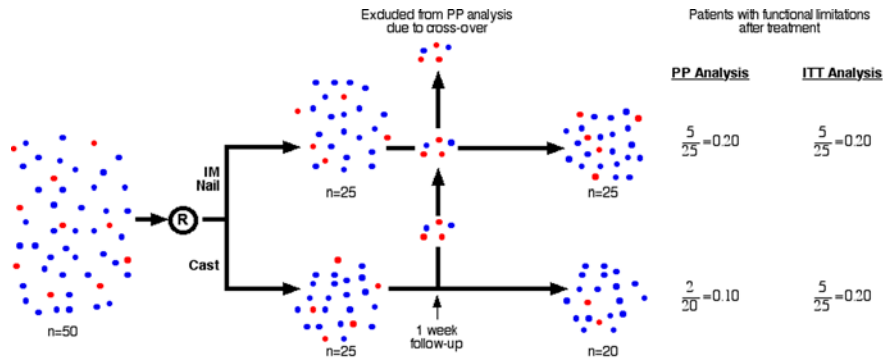


Fig. 1

Hypothetical trial of treatment with a cast compared with an intramedullary (IM) nail for low-energy fractures of the tibia. Both treatments are assumed to be equivalent. Fifty patients are enrolled and equally randomized between the two groups. The end point of the study is the number of patients returning to “normal” function. Ten patients (red dots) are unmotivated and would do poorly despite treatment allocation, and randomization equally distributes these patients between the two groups. All patients in the intramedullary nail group have uneventful surgery. Five patients in the cast group return at one week and want intramedullary nailing. Three of these five are unmotivated. At the end of the trial, all unmotivated patients have functional limitations regardless of the treatment they received. With use of a per-protocol analysis, the five patients who cross over are excluded. The treatment groups are no longer balanced. Two (10%) of the twenty patients in the cast group and five (20%) of the twenty-five in the intramedullary nail group are unmotivated and have limitations. It appears as if cast treatment is superior. In reality, the unmotivated patients would do poorly regardless of the treatment they receive. With the application of the intention-to-treat principle, the patients who cross over are analyzed in their original randomization group. As a result, an equal number of patients (20%) in the two treatment groups have limitations. This is what we expect. PP = per protocol, ITT = intention-to-treat, and R = randomization.

number of patients who have limitations are equal (20%) in the two groups (five of twenty-five in each group). This is what we expect as we know that unmotivated patients do poorly despite treatment with a cast or an intramedullary nail.

Some investigators analyze patients according to the treatment they actually received rather than exclude them as in a per-protocol analysis. This is known as treatment-received analysis². Let us consider what happens if the five

patients who cross over from cast treatment to intramedullary nailing are analyzed as patients in the intramedullary nail group (Fig. 2). Two (10%) of twenty patients in the cast group and eight (27%) of thirty patients in the intramedullary nail group are unmotivated and do poorly. This worsens the bias, and it now appears as if cast treatment is far superior. An intention-to-treat analysis again solves this problem.

A patient can initiate crossover in

treatment as the previous example illustrates. What happens when a surgeon needs to change a patient’s randomized treatment? Consider a randomized trial of reamed compared with unreamed nailing for diaphyseal fractures of the tibia. A patient randomized to unreamed nailing has a canal that is too narrow for the smallest nail. This is discovered intraoperatively as the surgeon attempts to pass the nail. In this situation, the patient was prematurely randomized into

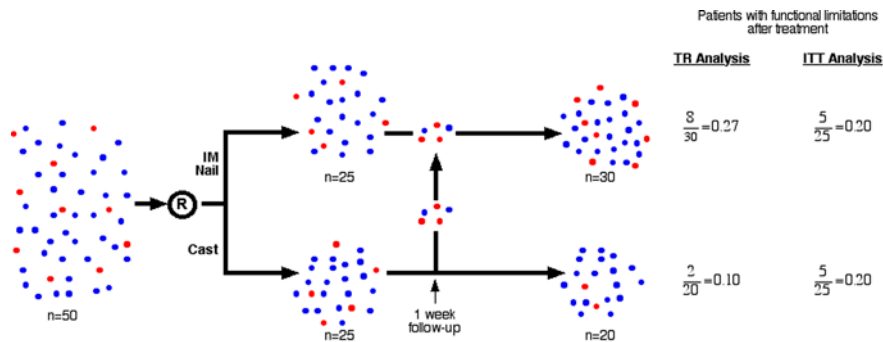


Fig. 2

The same hypothetical trial of treatment with a cast compared with an intramedullary (IM) nail for low-energy fractures of the tibia. In this case, the patients who cross over from treatment with a cast to intramedullary nailing are analyzed according to the treatment received. Two (10%) of twenty in the cast group and eight (27%) of thirty in the intramedullary nailing group are unmotivated and have functional limitations. It again appears as if cast treatment is superior. With use of an intention-to-treat analysis, an equal number of patients (20%) have limitations and both treatments are equivalent. This is again what we expect. A red dot indicates an unmotivated patient. TR = treatment received, ITT = intention-to-treat, and R = randomization.

the trial⁶. Ideally, it should have been identified that the patient was not a candidate for unreamed nailing and should never have been included in the study. In other words, a patient must be equally eligible for both interventions to be randomized. This patient never received the randomized intervention (i.e., unreamed nailing) and thus was inappropriately included initially and can be excluded from the analysis of data⁶.

Intention-to-treat analysis provides a conservative estimate of treatment effect, as this effect is diluted because of noncompliance⁵. It may, however, underestimate the magnitude of treatment effect in compliant patients when noncompliance is considerable¹. For example, imagine a pill that completely prevents deep vein thrombosis after total hip arthroplasty. Only 50% of patients are compliant with treatment, and none have deep vein thrombosis develop. The other 50% are noncompliant, and half of them have deep vein thrombosis develop. With an intention-to-treat analysis, it appears as if the medication is 75% effective (50% + 25%). In reality, the pill is 100% effective and the treatment effect is grossly underestimated because of noncompliance.

The best way to deal with noncompliance is to design a study to minimize it. An intention-to-treat analysis attempts to correct statistically for protocol violation, but it does not redeem problems with study design^{3,7}. Therefore, randomization should be done as close as possible in time to the intervention to minimize crossover, study participants should be blinded to the treatment they will receive, and surgeons should be sufficiently skilled to perform either of the treatments the patient may be randomized to receive. By maximizing compliance with the

original randomization assignments, bias in the analysis of the results is minimized. In addition, the method of randomization should be truly random. For example, subjects should be randomized to treatment group by sequential envelope or random-number assignment rather than by subject surname or day of the week.

As can be seen, an intention-to-treat approach is not a remedy for unsound design or incomplete follow-up. In fact, substantial loss to follow-up alters the initial randomization and introduces exactly the same bias as a per-protocol analysis¹. One cannot assume that all patients who are lost to follow-up do well. A conservative approach is to assume that all patients who are lost to follow-up do poorly. The truth is somewhere between “all patients do well” and “all patients do poorly.” This is known as a sensitivity analysis. An acceptable number of patients lost to follow-up depends on the individual study. The more subjects who are lost to follow-up, the greater the chance that the results are biased⁴. If a sensitivity analysis was not performed in a trial, clinicians can decide for themselves if the number of subjects lost to follow-up is excessive. This can be done by recalculating the results with use of the assumption that all of the missing subjects did poorly or did well. If the results are not changed with these calculations, then the number of subjects lost to follow-up was not excessive⁴.

There are other approaches to deal with missing data, but all are imperfect and a full discussion of this problem is beyond the scope of this article. In summary, the results from studies with substantial loss to follow-up are weaker, and an intention-to-treat analysis cannot eliminate bias in this situation⁷.

In conclusion, intention-to-treat analysis compares study groups in terms of the treatment to which they were randomly allocated, regardless of the treatment they actually received. This preserves randomization and minimizes bias. Intention-to-treat analysis provides a conservative estimate of treatment effect; however, the underestimation can be substantial when noncompliance is high. As such, noncompliance should be kept to a minimum through the study design, as intention-to-treat analysis “cannot redeem poor quality data resulting from inadequate design or implementation of a study.”³ Nonetheless, intention-to-treat analysis has an important role to play in the analysis of data from randomized clinical trials as it minimizes bias and provides a better estimate of the true treatment effect.

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