

## Intention To Treat: Once Randomized, Always Analyzed

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The expression "intention-to-treat analysis" probably first appeared in print in Bradford Hill's (1961) *Principles of Medical Statistics*. Essentially, the phrase means that all patients randomly allocated to one of the treatments in a clinical trial should be analyzed together as representing that treatment, whether or not they completed, or indeed received, that treatment (Newell, 1992).

Random assignment to treatment and no-treatment groups and analysis of results on only those patients who received the amount and type of treatment prescribed is considered biased by those who advocate intention-to-treat analysis (Lee, Ellenberg, Hirtz, & Nelson, 1991; Collins & Dorus, 1991). Conversely, clinicians may find the intention-to-treat approach intuitively offensive. Determining the success or failure of a treatment based on results of some patients who did not receive it or who did not receive the amount prescribed seems illogical.

The purposes of this paper are to explore the reasons for intention-to-treat analysis, discuss the problems that arise with it, examine the influence that failure to perform intention-to-treat analysis may have had on the results of recent aphasia treatment trials, and suggest means for coping with the demands for intention-to-treat analysis in future aphasia treatment trials. For the purpose of this discussion, *compliant patients* are defined as those who received the amount and type of treatment prescribed. *Noncompliant patients* are those who completed the study but did not receive the amount and/or type of treatment prescribed. *Dropouts* are those who did not complete the study and, therefore, did not receive the amount of treatment prescribed. *As-treated patients* are those who were assigned to a specific treatment and did

not complete that treatment or who "crossed over" and received another treatment.

## **WHY INTENTION-TO-TREAT ANALYSIS?**

Reasons for intention-to-treat analysis include maintaining prognostic balance, preserving sample size, and the difficulty in defining compliance.

### **Prognostic Balance**

Patients are the same only at the time of randomization. Excluding noncompliant patients and dropouts may create important prognostic differences among treatment groups. For example, in aphasia treatment trials, excluding these patients from analysis may result in significant group differences in variables that are believed to influence response to treatment—time postonset, severity, size and site of lesion, and so forth. Furthermore, patients may be noncompliant or drop out because of their response to treatment. For example, those who are making less progress attend treatment less often or drop out.

### **Sample Size**

Excluding noncompliant patients and dropouts from analysis may significantly reduce sample size and, consequently, reduce statistical power. This practice results in an unacceptable increase in the probability of a Type II error, the error of accepting a false hypothesis.

### **Compliance**

Some researchers (Armitage, 1979; Haynes & Dantes, 1987) have argued that results on compliant patients cannot be generalized to all people with the same disorder, because the majority of people will be noncompliant under "usual" circumstances. Moreover, it is difficult to define "compliance." For example, Lincoln et al. (1984) prescribed 2 hours of aphasia treatment each week for 24 weeks. As shown in Table 1, only 26% of their sample received even close to the amount of treatment prescribed. In one analysis, the authors included all patients assigned to treatment regardless of the amount of treatment received.

**Table 1. Difficulty in Defining Compliance Based on the Amount of Treatment Received**

<i>No. Sessions</i>	<i>No. Patients (N = 104)</i>	<i>% Patients</i>
0-12	39	38
13-24	16	15
25-36	22	21
37-48	27	26

Adapted from "Effectiveness of Speech Therapy for Aphasic Stroke Patients: A Randomized Controlled Trial" by N. B. Lincoln et al., 1984, *The Lancet*, 1, pp. 1197-1200.

A subsequent analysis included patients who completed at least half of their assigned treatment.

## **OBJECTIONS TO INTENTION-TO-TREAT ANALYSIS**

Several objections to intention-to-treat analysis appear reasonable. First, calling a patient treated who in fact was not indicates very little about the efficacy of treatment. Second, mixing noncompliant patients, dropouts, and compliant patients in the analysis introduces heterogeneity that controlled treatment trials attempt to avoid. There are numerous reasons patients fail to comply or drop out. Some simply quit, others die, some become ill, and others experience events that make them different from the way they were when they met selection criteria (e.g., they suffer another stroke). Third, end-point data will differ markedly among compliant patients, noncompliant patients, and dropouts. For example, compliant patients will have completed all evaluations, noncompliant patients will have completed all or only some, and dropouts may have completed only one (the pretreatment evaluation).

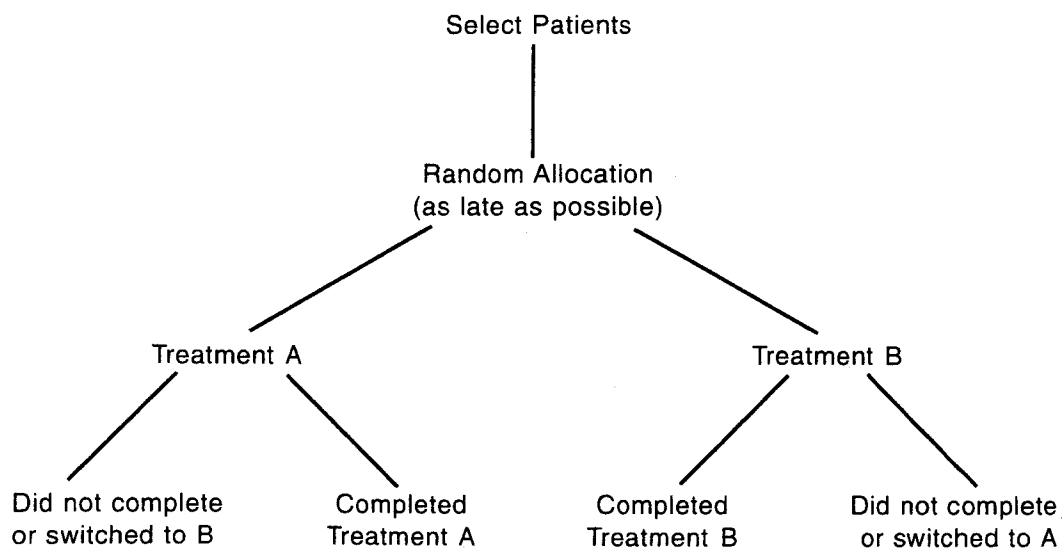
## **ALTERNATIVES TO INTENTION-TO-TREAT ANALYSIS**

The intention-to-treat analysis is not the only option for analysis. At least three types of analyses are available: intention-to-treat, compli-

ant patients only, and as-treated. Intention-to-treat analysis includes all patients who were randomized. This is also known as a "pragmatic trial," a "program effectiveness analysis," and an "effectiveness analysis." A compliant patients-only analysis includes only those patients who comply with the treatment regimen to which they were assigned. This is also known as an "explanatory trial," a "test of biological efficacy analysis," and an "efficacy analysis." An as-treated analysis includes patients according to the treatment received regardless of the regimen to which they were assigned. It includes patients who do not complete the trial and those who switch from one treatment to another. It is also known as a "treatment received analysis" and a "garbage analysis" (Newell, 1992).

How do these analyses influence results? Figure 1 shows a schema for a randomized trial. Patients who meet selection criteria are assigned randomly to either Treatment A or Treatment B. As the trial progresses, some patients receive the treatment to which they were assigned. Other patients, however, either (a) do not receive the treatment to which they were assigned or (b) switch to the other treatment. How might these patients influence results?

Table 2 shows data from an early comparison between coronary artery bypass surgery and medical treatment. Of the 373 patients allocated



**Figure 1.** A simplified schema for a randomized controlled trial. (Adapted from "Intention-to-Treat Analysis: Implications for Quantitative and Qualitative Research" by D. J. Newell, 1992, *International Journal of Epidemiology*, 21, pp. 837-841.) Reprinted by permission of Oxford University Press.

**Table 2. Numbers of Survivors and Deaths 2 Years After Allocation to Carotid Artery Bypass Surgery or Medical Treatment**

	<i>Allocated to Medicine</i>		<i>Allocated to Surgery</i>	
	<i>Received Surgery</i>	<i>Received Medicine</i>	<i>Received Surgery</i>	<i>Received Medicine</i>
Survived 2 years	48	296	354	20
Died	2	27	15	6
Total	50	323	369	26

From "Intention-to-Treat Analysis: Implications for Quantitative and Qualitative Research" by D. J. Newell, 1992, *International Journal of Epidemiology*, 21, pp. 837-841. Reprinted by permission of Oxford University Press.

to medical treatment, 50 switched to surgical treatment and, of those, only 2 died. Of the 395 allocated to surgery, 26 received medical treatment and, of those, 6 died. Table 3 compares the study's results using the three different analyses. Intention-to-treat analysis shows no significant difference in 2-year mortality rates between the two treatments, surgery versus medicine. A compliant patients-only analysis shows a significantly lower 2-year mortality rate in the patients treated with surgery. An as-treated analysis wildly exaggerates the apparent value of surgery. The same data analyzed three different ways yield three different results.

## INTENTION-TO-TREAT ANALYSIS AND APHASIA TREATMENT TRIALS

A review of recent aphasia treatment trials (see Table 4) indicates that none has reported an intention-to-treat analysis. Thus, the results of all would be rejected by those who insist on intention-to-treat analysis.

Basso, Capitani, and Vignolo (1979) conducted what appears to be a retrospective comparison of treated patients and self-selected no-treatment patients. Their initial sample size, 281 patients, was reduced to 193 patients in some analyses. Thus, patients with missing data—perhaps noncompliant patients and dropouts—were not analyzed in some comparisons. No intention-to-treat, dropout, or as-treated analyses are reported; thus, the reader does not know whether compliant patients differed on important prognostic variables from those who did not comply or who dropped out.

**Table 3. Two-Year Mortality Rates in Comparison Between Carotid Artery Bypass Surgery and Medical Treatment as Determined by Three Analyses**

<i>Analysis by</i>	<i>Allocated to</i>		$\chi^2$	<i>p</i>
	<i>Medicine</i>	<i>Surgery</i>		
Intention-to-treat	7.8%	5.3%	1.9	.17
Compliant patients only	8.4%	4.1%	5.6	.018
As-treated	9.5%	4.1%	9.1	.003

Adapted from "Intention-to-Treat Analysis: Implications for Quantitative and Qualitative Research" by D. J. Newell, 1992, *International Journal of Epidemiology*, 21, pp. 837-841. Reprinted by permission of Oxford University Press.

**Table 4. Sample Size in Selected Aphasia Treatment Trials**

<i>Study</i>	<i>Sample Size</i>	<i>No. Dropouts</i>	<i>% Dropouts</i>
Basso et al. (1979)	281	0-88 <sup>a</sup>	0-31
Lincoln et al. (1984)	327	166	51
Shewan and Kertesz (1984)	100	21 <sup>a</sup>	21
Wertz et al. (1986)	121	27	22

<sup>a</sup>The number varied for some analyses.

Lincoln et al. (1984) assigned patients randomly to treatment and no-treatment groups. Of the 327 patients who were randomly assigned, 161 completed the treatment trial. Noncompliant patients—those who did not receive the amount of treatment prescribed—were included in the outcome analysis, but it is not clear whether dropouts were included. No analysis of prognostic differences among compliant, noncompliant, and dropout patients was reported.

Shewan and Kertesz (1984) assigned patients randomly to three treatment groups and included a self-selected no-treatment group. "Exit criteria"—recovery, death, occurrence of a second stroke, prolonged illness, and so on—excluded 21 patients from the outcome analyses. Sample sizes varied across analyses, implying that all patients were not included in every analysis. No comparison of prognostic differences among compliant, noncompliant, and dropout patients was reported.

The second Veterans Administration (VA) Cooperative Study (Wertz et al., 1986) assigned patients randomly to two treatment groups and a no-treatment group. Twenty-seven of 121 patients entered were considered dropouts. Attrition was not related to group assignment, and the

most common reasons for dropping out were illness that prevented completing the prescribed treatment and the occurrence of a second stroke. A dropout analysis comparing patients who remained in the study with those who dropped out was conducted but not reported. Similarly, an intention-to-treat analysis was conducted but, because results did not differ from the compliant patients-only analysis, it was not reported.

Again, those who advocate intention-to-treat analysis would reject the reported results of the aphasia treatment trials. Is this reasonable? Probably. It is not sufficient to demonstrate that aphasia treatment *can* work, using a compliant patients-only analysis. It is equally important to determine whether aphasia treatment *does* work, using an intention-to-treat analysis.

## COPING WITH INTENTION-TO-TREAT ANALYSIS

How do researchers cope with the demands for intention-to-treat analysis and, at the same time, determine whether aphasia treatment is efficacious? The answer, probably, is to conduct multiple analyses. These include intention-to-treat, to determine the treatment's effectiveness and satisfy the scientific community; compliant patients only, to determine the treatment's efficacy; as-treated, to determine what actually happened in the treatment trial; and dropout, to assist in monitoring the safety of the treatment or treatments and to assist in analyzing the results of the as-treated analysis.

Multiple analyses generate multiple requirements. First, it is necessary to estimate sample size for both an intention-to-treat analysis and a compliant patients-only analysis to ensure sufficient statistical power for the latter. This approach was used in the second VA Cooperative study, where the anticipated dropout rate was considered in estimating sample size.

Second, it is essential to collect outcome measures on all noncompliant and dropout patients, whenever possible, to achieve some control over time in the end-point analyses. For example, one should attempt to follow these patients with the prescribed evaluations even though they are no longer participating in treatment.

Finally, it is necessary to provide a strict definition of compliance. This should include not only the amount of treatment received, but also its duration and intensity.

There is no one way of satisfying everyone. Conducting intention-to-treat *and* compliant patients-only analyses may dull disagreement. Both provide more information than either alone. Intention-to-treat

analysis tells about life, whereas a compliant patients-only analysis tells about how life could be. Certainly, no matter how hard one tries, conducting controlled, aphasia treatment trials is not getting easier.

## REFERENCES

- Armitage, P. (1979). The analysis of data from clinical trials. *The Statistician*, 28, 171-183.
- Basso, A., Capitani, E., & Vignolo, L. A. (1979). Influence of rehabilitation on language skills in aphasia patients: A controlled study. *Archives of Neurology*, 36, 190-196.
- Collins, J. F., & Dorus, W. (1991). Patient selection bias in analyses using only compliant patients. In J. A. Cramer & B. Spiker (Eds.), *Patient compliance in medical practice and clinical trials* (pp. 335-348). New York: Raven Press.
- Haynes, R. B., & Dantes, R. (1987). Patient compliance and the conduct and interpretation of therapeutic trials. *Controlled Clinical Trials*, 8, 12-19.
- Hill, A. B. (1961). *Principles of medical statistics* (7th ed.). London: The Lancet.
- Lee, Y. J., Ellenberg, J. H., Hirtz, D. G., & Nelson, K. B. (1991). Analysis of clinical trials by treatment actually received: Is it really an option? *Statistics in Medicine*, 10, 1595-1605.
- Lincoln, N. B., Mulley, G. P., Jones, A. C., McGuirk, E., Lendrem, W., & Mitchell, J. R. A. (1984). Effectiveness of speech therapy for aphasic stroke patients: A randomized controlled trial. *The Lancet*, 1, 1197-1200.
- Newell, D. J. (1992). Intention-to-treat analysis: Implications for quantitative and qualitative research. *International Journal of Epidemiology*, 21, 837-841.
- Shewan, C. M., & Kertesz, A. (1984). Effects of speech and language therapy on recovery from aphasia. *Brain and Language*, 23, 272-299.
- Wertz, R. T., Weiss, D. G., Aten, J. L., Brookshire, R. H., Garcia-Bunuel, L., Holland, A. L., Kurtzke, J. F., LaPointe, L. L., Milianti, F. J., Brannegan, R., Greenbaum, H., Marshall, R. C., Vogel, D., Carter, J., Barnes, N. S., & Goodman, R. (1986). Comparison of clinic, home, and deferred language treatment for aphasia. *Archives of Neurology*, 43, 653-658.