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Making Sense of Biostatistics: As-Treated and Intention-to-Treat Analysis

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Randomized clinical trials are so powerful because they randomly assign subjects to the treatment and control groups. At the end of the study, the biostatisticians can compare the safety and effectiveness of the treatment versus the control using statistical techniques that are valid only if the subjects are randomized.

So far, so good, but what do we do with data from subjects who drop out of the study, do not adhere to treatment regimens, or otherwise deviate from the protocol? These deviations might not be random. For example, subjects in the treatment group might drop out because they experience unpleasant side effects, or subjects in the placebo group might drop out because they see no improvement in their health. These deviations might occur more frequently in different groups, e.g., depending on concomitant medications or the initial severity of the condition.

Prior to starting the study, the researchers must decide what to do with the data from subjects who deviate from the protocol. There are two primary options:

- **As-treated.** Analyze study data only from subjects who complete the study and adhere to protocol requirements.
- **Intention-to-treat.** Analyze study data from all subjects, regardless of whether they complete the study and adhere to protocol requirements.

As-treated analysis has the advantage of examining only those subjects with complete data. However, because of the reasons cited above, as-treated analysis is prone to numerous, potentially important biases. The results have suggestive value but simply cannot be trusted.

Intention-to-treat (ITT) analysis preserves randomization but has the significant disadvantage of assuming what simply is not so — that the subjects adhere to the protocol and take all their doses on schedule. It therefore understates the treatment effect. We cannot demonstrate the advantages of a new drug if the subjects do not take it. With ITT analysis, it is thus imperative to design and conduct studies for maximum subject retention and adherence.

The Coronary Drug Project (1966-1975) compared the five-year mortality rate between subjects treated with clofibrate versus placebo following an initial heart attack. For subjects randomly assigned to clofibrate, the five-year mortality rate was 18%, versus 19% in subjects randomly assigned to placebo. However, the investigators discovered that many of the subjects assigned to clofibrate did not comply with their treatment (i.e., took less than 80% of their tablets). In fact, the five-year mortality rate was substantially different between clofibrate compliers (15%) versus noncompliers (25%). This was an exciting finding because it appeared to show that patients who take the drug as prescribed can expect a 40% reduction in mortality. However, on closer inspection, it turned out that subjects in the placebo group who complied with the protocol saw the same reduction in mortality. In other words, the compliers had some other unknown characteristic that improved their life expectancy versus non-compliers. Perhaps the health of the subjects drove compliance/noncompliance, rather than the other way around.

ITT analysis has a second advantage: It estimates the treatment effect in real-world clinical practice, where patients do not always adhere to treatment regimens. ITT analysis is thus

equivalent to comparing *treatment policies* rather than comparing *treatments*. In other words, if patients do not take their pills, e.g., because they cause nausea, it does not really matter how effective the treatment is in the controlled environment of clinical trials.

For these reasons, primary analysis of the data should use the ITT method. The as-treated method can be used for secondary analyses, e.g., of the likelihood and potential effects of nonadherence across subgroups. In performing as-treated analyses, we lose the comparability ensured by randomization. The results are thus more speculative and best suited for generating new hypotheses for future study.

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