But these deviations are likely to be inconsequential because they do not exclude subjects who had experienced an adverse event, or subjects who had dropped out of the study.

What was defined above as ITT analysis, in the above examples from various clinical trials, actually fell under one of two other concepts. The first concept was *modified ITT analysis*, and the second concept was *per protocol analysis*. If a publication establishes that analysis was by modified ITT analysis (as was the case in the publications mentioned above), then the reader will realize that the results may have been subjected to bias, and will be able to take into account the possibility that certain biases may have crept into the results.

A survey of published clinical trials by Altman et al. (15) distinguishes between ITT analysis and per protocol analysis. According to these authors, of 119 reports stating that all participants were included in the analysis in the groups to which they were originally assigned, 15 (13%) failed to include all of the allocated patients in the analysis. Furthermore, according to these authors, excluding a subject after randomization, for the reason of failing to meet the inclusion/exclusion criteria, is "contrary to the intent to treat principle." The resulting analysis is properly classified as per protocol analysis.

In a survey by Gravel et al. (16) of 249 clinical trials that reported using ITT analysis, 7% of these (17 trials) actually used per protocol analysis. Gravel et al. (17) concluded that these 17 trials clearly violated the requirements of ITT analysis. In a survey of 81 published studies on arthritis clinical trials, Baron et al. (18) found that ITT analysis was performed in only six of the studies, and PP analysis was performed in 48 of the studies.

II. ITT ANALYSIS CONTRASTED WITH PP ANALYSIS

Per protocol (PP) analysis means including, in the analysis, only subjects who were enrolled in the clinical trial, and who actually complied with all of the substantive instructions set forth in the Clinical Study Protocol. In one of its Guidance for Industry documents, the FDA defines per protocol analysis as, "[t]he set of data generated by the subset of subjects who complied with the protocol sufficiently to ensure that these data would be likely to exhibit the effects of treatment according to the

[15] Altman DG, Schulz KF, Moher D, et al. The revised CONSORT statement for reporting randomized trials: explanation and elaboration. *Ann Intern Med.* 2001;134:663–694.

[16] Gravel J, Opatrny L, Shapiro S. The intention-to-treat approach in randomized controlled trials: are authors saying what they do and doing what they say? *Clin Trials.* 2007;4:350–356.

[17] Gravel J, Opatrny L, Shapiro S. The intention-to-treat approach in randomized controlled trials: are authors saying what they do and doing what they say? *Clin Trials.* 2007;4:350–356.

[18] Baron G, Boutron I, Giraudeau B, Ravaud P. Violation of the intent-to-treat principle and rate of missing data in superiority trials assessing structural outcomes in rheumatic diseases. *Arthritis Rheum.* 2005;52:1858–1865.