trial, as follows. Trials without exclusions more often report imputations of missing data than those with exclusions. In other words, missing values were replaced by the last value observed. This method is popular for imputation of missing data, but leads to overly precise estimates and to bias.

IV. RUN-IN PERIOD, AS PART OF THE STUDY DESIGN, IS RELEVANT TO ITT ANALYSIS AND PP ANALYSIS

Montori and Guyatt (30) teach that the bias introduced when using a per protocol analysis can be overcome where the schema of a clinical trial uses a run-in period. According to these authors, this type of study design ensures maximal adherence in the time period following the start date. A run-in period can identify non-adherent subjects or non-compliant subjects, so they can be excluded before randomization. With this type of study design, only subjects successfully adhering to the requirements set forth during the run-in period are included in the ITT population.

One form of study design, which takes the form of a run-in period, is to identify potential subjects for enrolling in a clinical trial, to initiate drug treatment, and to order time-consuming diagnostic tests. Once the time-consuming diagnostic tests have been completed, the subjects are then formally enrolled in the clinical trial. Using this form of study design, the investigators can refer to their analysis as ITT analysis (while avoiding using the term *modified ITT analysis*). This form of study design was used by Schutz et al. (31) in a study of leukemia, where the time-consuming diagnostic test involved chromosomal analysis. The time-consuming test took the form of histological techniques to identify the Philadelphia chromosome, a conventional diagnostic test for acute lymphoblastic leukemia (ALL). Chemotherapy was initiated with all potential study subjects, followed by starting work on the time-consuming histological tests. Only those potential study subjects proven to bear the Philadelphia chromosome were actually enrolled in the trial, and were considered to be part of the ITT population. The chemotherapy that was administered during the run-in period was vincristine, asparaginase, and prednisone or dexamethasone (32).

[30] Montori VM, Guyatt GH. Intention-to-treat principle. *Can Med Assoc J.* 2001;165:1339–1341.

[31] Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. *J Clin Oncol.* 2009;27:5175–5181.

[32] Schultz KR, Bowman WP, Aledo A, et al. Improved early event-free survival with imatinib in Philadelphia chromosome-positive acute lymphoblastic leukemia: a children's oncology group study. *J Clin Oncol.* 2009;27:5175–5181.