d. ITT Analysis Versus PP Analysis—The Berthold Study

In a study of a natural product tested for lowering cholesterol, Berthold et al. (26) defined the PP population. Patients were classified as nonadherent if they failed to take at least 80% or took more than 120% of the prescribed dose. Adherence was checked by pill count at visit four (day 0) for the placebo run-in phase and at visit five (6 weeks) and visit six (12 weeks) for the treatment phase. Patients found not to have adhered to the clinical trial regimen at visits five or six were not included in the PP analysis. One hundred and forty-three subjects were used for the ITT analysis, while 129 were used for the PP analysis. The authors found no differences in the results, with either analysis.

e. ITT Analysis Versus PP Analysis—The Geddes Study

Geddes et al. (27) defined PP analysis as all treated subjects with clinical signs and symptoms of sepsis and proven infection, excluding major protocol violators. Major protocol violators, who were not included in the PP population, were subjects with incorrect entry diagnosis, incorrect treatment duration, antibiotic pretreatment, or a missing posttreatment clinical evaluation. The investigators conducted both ITT analysis and PP analysis in their clinical study of two different antibiotic treatments. According to ITT analysis, the cure rate for levofloxacin (77%) was higher than that for imipenem/cilastatin (68%). According to PP analysis, the cure rate for levofloxacin (89%) was similar to that for imipenem/cilastatin (85%). Thus, the Geddes study documents an example where ITT analysis and PP analysis resulted in different conclusions regarding efficacy.

III. DISADVANTAGES OF ITT ANALYSIS

Most comments regarding ITT analysis versus PP analysis dwell on biases that occur with use of PP analysis. But biases can also result when ITT analysis is used. According to Nüesch et al. (28), ITT analysis can introduce bias into the analysis of the clinical 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.

Also, as detailed later in this chapter, ITT analysis can be misleading where subjects are enrolled on an emergency basis before it can be confirmed that the study subject actually has the suspected disease.

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[27]Geddes A, Thaler M, Schonwald S, Härkönen M, Jacobs F, Nowotny I. Levofloxacin in the empirical treatment of patients with suspected bacteraemia/sepsis: comparison with imipenem/cilastatin in an open, randomized trial. J. Antimicrob. Chemother. 1999;44:799–810.

[28]Nüesch E, Trelle S, Reichenbach S, et al. The effects of excluding patients from the analysis in randomised controlled trials: meta-epidemiological study. Brit. Med. J. 2009;339:b3244.