Le Henanff et al. (20) defined PP analysis, and distinguished it from ITT analysis, as follows. According to these authors, ITT analysis includes all subjects, regardless of their compliance with the entry criteria, treatment actually received, withdrawal from treatment, or deviation from the protocol while, in contrast, PP analysis includes only subjects who satisfied the entry criteria of the trial and who completed the treatment as defined in the Clinical Study Protocol.

The appeal of performing PP analysis is intuitive, and easy for any layperson to understand. According to the European Medicines Agency (EMA) (21), Per protocol analysis can maximize the opportunity for a new treatment to show additional efficacy in the analysis. PP analysis most closely reflects the scientific basis underlying the study design for the clinical trial.

However, the EMA (22) cautions that, regarding the use of PP analysis, "[h]owever, the corresponding test of the hypothesis and estimate of the treatment effect may or may not be conservative depending on the trial; the bias, which may be severe, arises from the fact that adherence to the study protocol may be related to treatment and outcome. The problems that lead to the exclusion of subjects to create the PP set, and other protocol violations, should be fully identified and summarised."

Per protocol analysis can result in bias as follows. If a subject experiences severe adverse events, and refuses to comply with the dosing protocol, or is not able to comply with an appointment at the clinic, exclusion of this subject from the trial's analysis will prevent the trial from accomplishing it goal of detecting adverse events. In this way, PP analysis can make a study drug appear safer than it really is.

a. ITT Analysis Versus PP Analysis—The Molina Study

In a clinical trial on *Trypanosoma cruzi* infections, Molina et al. (23) used both ITT analysis and PP analysis. The group used for PP analysis was defined as all enrolled patients, but excluding "patients who were lost to follow-up, those who dropped out owing to adverse events," as well as patients where the drug actually failed in treating the infection, as determined by measuring the trypanosomal DNA in the bloodstream. The clinical trial was actually on patients with Chagas' disease, which is caused by *T. cruzi*.

This clinical trial is unusual, in that the results from ITT analysis and PP analysis were dramatically different. The following explores the results only from the active control group, which used a drug that was established as effective, namely, benznidazole. In the ITT group, the active control was shown to be effective in 61.6% of the patients, while in the PP group, the active control worked in 94.4% of the patients. This difference is notable, in view of the author's finding that in most clinical trials that include both ITT analysis and PP

[20]Le Henanff AL, Giraudeau B, Baron G, Ravaud P. Quality of reporting of noninferiority and equivalence randomized trials. J. Am. Med. Assoc. 2006;295:1147–51.

[21]European Medicines Agency (EMEA) ICH Topic E9 Statistical Principles for Clinical Trials; September 1998.

[22]European Medicines Agency (EMEA) ICH Topic E9 Statistical Principles for Clinical Trials; September 1998.

[23]Molina I, Prat J, Salvador F, et al. Randomized trial of posaconazole and benznidazloe for chronic Chagas' disease. New Engl. J. Med. 2014;370:1899–908.