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Methodological Challenges in Analyzing Patient-Reported Outcomes in a Clinical Trial

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The analysis of patient-reported outcomes (PRO) data in an international clinical trial presents methodological, statistical and interpretive challenges. Specific strategies are needed regarding the psychometric measurement properties of self-report instruments, cross-cultural measurement equivalence, definitions of clinical significance, missing data, longitudinal modeling, and descriptions of clinically interpretable results. Development and implementation of these strategies is illustrated using the 16-country International Randomized IFN vs. STI571 (IRIS) Study of 1106 newly diagnosed patients with chronic phase chronic myeloid leukemia. The primary endpoint was the duration of progression-free survival; PROs were secondary endpoints. Crossover to the other treatment was permitted because of intolerance or lack of efficacy. The Functional Assessment of Cancer Therapy-Biologic Response Modifiers (FACT-BRM) was completed as a measure of health-related quality of life at baseline, months 1–6, 9, 12, 18, and 24 in the patient's preferred language. The methodological issues and specific strategies developed to address them are summarized. An item response theory (IRT) measurement model was used to evaluate psychometrics, including cross-cultural comparability (eight languages), and to aid in interpretation of treatment differences. A mixed effects model was chosen for the longitudinal analyses, with a pattern-mixture technique to adjust for nonignorable missing data. Crossover effects were added as a time-dependent covariate. To better understand the meaning of the PRO scores, a clinically significant treatment effect was prespecified, and a modified forest plot was used to summarize IRT responses. 1049 patients (95%) participated in the assessments. The patterns of dropout and change were quite different for the treatment arms. This study presented major methodological challenges to PRO data analysis, all of which were addressed using state-of the-art modeling techniques. The analysis plan and results may be useful for statisticians, researchers and clinicians who analyze and interpret PROs.