Wanjie Sun, J Bioanal Biomed 2019, Volume 11
DOI: 10.4172/1948-593X-C1-047

Estimation of causal equivalence effects in clinical bioequivalence/biosimilar studies in the presence of inter current events: Noncompliance and missing data

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In equivalence, biosimilar, and non-inferiority studies, intent-to-treat (ITT) analysis tends to make the two treatments look similar, thereby is generally anti-conservative. The Per Protocol (PP) analysis based on completers and compliers is more able to reflect treatment differences and is usually preferred in equivalence assessment. In clinical endpoint bioequivalence studies, the current primary analysis for assessing equivalence between a generic and an innovator product is usually based on the observed per-protocol (PP) population. However, missing data and non-compliance are post-randomization intercurrent events and may introduce selection bias. Therefore, PP analysis is generally not causal. The FDA Missing Data Working Group (2016) recommended using "causal estimands of primary interest." In this paper, we propose a principal stratification causal framework and co-primary causal estimands to test equivalence, which was one of the approaches recommended by the recently published ICH E9 (R1) addendum to address intercurrent events. We identify three conditions under which the current PP estimator is unbiased for one of the proposed co-primary causal estimands-the "Survivor Average Causal Effect" (SACE) estimand. Simulation shows that when these three conditions are not met, the PP estimator is biased, and may inflate Type 1 error and/or change power. We also propose a tipping point sensitivity analysis to evaluate the robustness of the current PP estimator in testing equivalence when the sensitivity parameters deviate from the three identified conditions, but stay within a clinically meaningful range. Our work is the first causal equivalence assessment in equivalence studies with intercurrent events and can be applied to comparative biosimilar clinical trials and non-inferiority trials.

Recent Publications:

1. Lou Y, Jones M P and Sun W (2018) Estimation of causal effects in clinical endpoint bioequivalence studies in the presence of intercurrent events: noncompliance and missing data. Journal of biopharmaceutical statistics 1-23.
2. LaVange L M and Permutt T (2016) A regulatory perspective on missing data in the aftermath of the NRC report. Statistics in Medicine 35(17):2853-2864.
3. Permutt T (2016) A taxonomy of estimands for regulatory clinical trials with discontinuations. Statistics in Medicine 35(17):2865-2875.
4. Permutt T (2016) Sensitivity analysis for missing data in regulatory submissions. Statistics in Medicine 35(17):2876-2879.
5. Sun W, Zhou L, Grosser S and Kim C (2016) A meta-analysis of missing data and non-compliance data in clinical endpoint bioequivalence studies. Statistics in Biopharmaceutical Research 8(3):334-344

Biography

Wanjie Sun is a Senior Mathematical Statistician at CDER of FDA. Prior to joining FDA, she worked at GWU as a Lead Research Scientist and a PI/co-PI for over ten years, and she also worked in pharmaceutical industry for a couple of years. She has obtained her PhD in Biostatistics at GWU. She has over 40 publications in statistical, medical, and pharmacy journals. Her research interests are in equivalence, non-inferiority, causal inference, study design, and missing data.