

TITLE: Calibrated Bayesian Noninferiority Inference for Paired Binary Endpoints Under Sparse Discordance

AUTHOR: Halim Halidola - BioNTech SE, Munich, Germany

ABSTRACT: Matched-pair noninferiority (NI) studies with binary endpoints are common in medical devices, diagnostic test evaluation, and crossover clinical trials where the same subject is evaluated using both test and reference products. Inference in these studies is driven primarily by discordant pairs, leading to challenges for standard asymptotic procedures **when sample sizes are small or discordant counts are sparse or zero**. Although Tango's score-based approach generally improves upon conventional Wald methods, finite-sample instability and interpretability challenges may remain in practice.

We propose a calibrated Bayesian framework for the design and analysis of paired binary NI studies based on the multinomial likelihood. NI is assessed using the posterior probability that the paired risk difference exceeds a prespecified NI margin. To align with regulatory expectations, the posterior decision criteria is calibrated through simulation to achieve nominal one-sided type I error control. Frequentist operating characteristics of posterior credible intervals are additionally evaluated. Weakly informative priors are used to stabilize estimation under sparse data without requiring continuity corrections. Simulation studies compare the proposed calibrated Bayesian procedure with Wald and Tango methods across varying sample sizes, discordance rates, and true differences between the groups.

Preliminary investigations suggest that the calibrated Bayesian approach maintains nominal type I error while providing stable interval estimation and competitive power relative to Tango's method, particularly in settings with very small sample sizes or rare discordant outcomes where asymptotic procedures may become unstable.

PRESENTING AUTHOR BIO: Halim Halidola (PhD) is Director of Biostatistics at BioNTech SE, Munich, Germany. His research interests include statistical methods for complex clinical trial designs, handling missing data, joint modeling of correlated endpoints, and non-inferiority and equivalence trial design.