Electronic Supplementary Material

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ESM1 File - Description of the Regression-Adjusted GPS (RGPS) signal detection methodology

The RGPS methodology operates by fitting separate Bayesian logistic regression models to each target adverse event. RGPS automatically selects two types of predictors to be included in each regression model: (1) products that are statistically associated with the target event, which are represented as indicator variables, and (2) stratification categories grouped by target event rates, which are represented as multiple regression intercepts.

Rather than using the fitted regression coefficients, e.g., odds ratios, to compute signal scores (disproportionalities), RGPS computes observed to expected ratios of counts similar to conventional methodologies. The expected counts are computed by summing the regression predicted probabilities of the target event across all reports mentioning the target product under the null hypothesis of no association between the target product and target event. The null

hypothesis probabilities are computed by setting the coefficient of the target product to zero if selected as a model predictor. This results in adjusted expected counts (background rates) that can address confounding and masking effects. The final signal score (and its confidence intervals) are computed using Bayesian smoothing of observed to expected counts similar to MGPS[1] and BCPNN[2]. Complete details of the RGPS methodology are presented in reference[3].

1. Dumouchel, W., *Bayesian Data Mining in Large Frequency Tables, with an Application to the FDA Spontaneous Reporting System.* The American Statistician, 1999. **53**(3): p. 177-190.
2. Bate, A., et al., *A Bayesian neural network method for adverse drug reaction signal generation.* Eur J Clin Pharmacol, 1998. **54**(4): p. 315-21.
3. DuMouchel, W. and R. Harpaz, *Regression-adjusted GPS algorithm (RGPS)*, in *Oracle White Paper, https://docs.oracle.com/health-sciences/empirica-signal-811/ESIUG/Regression-Adjusted_GPS_Algorithm.pdf*. 2012.