CHANGING THE COURSE OF HUMAN HEALTH THROUGH BOLD PURSUITS IN SCIENCE

Comparison of Bayesian Models for Detecting Safety Signals in Clinical Trials

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Overview

- The need to highlight and interpret properly adverse events reported from clinical trials
- Issues associated with highlighting adverse events in clinical study report
- Some methods to facilitate signal identification
- Performance measure for signal identification
- Comparison of the methods
- Recommendation

The recommended method can be used to effectively identify safety signals and help doctors and patients in healthcare management

Safety Writing of Clinical Trials Report

- Hundreds of adverse event terms are often reported in clinical trial
  - More safety tables than efficacy in typical Clinical Study Reports
- Critical for CSR to summarize and communicate safety findings
- Discussion of benefit risk is necessary in the context of disease setting, safety and efficacy of the experimental treatment

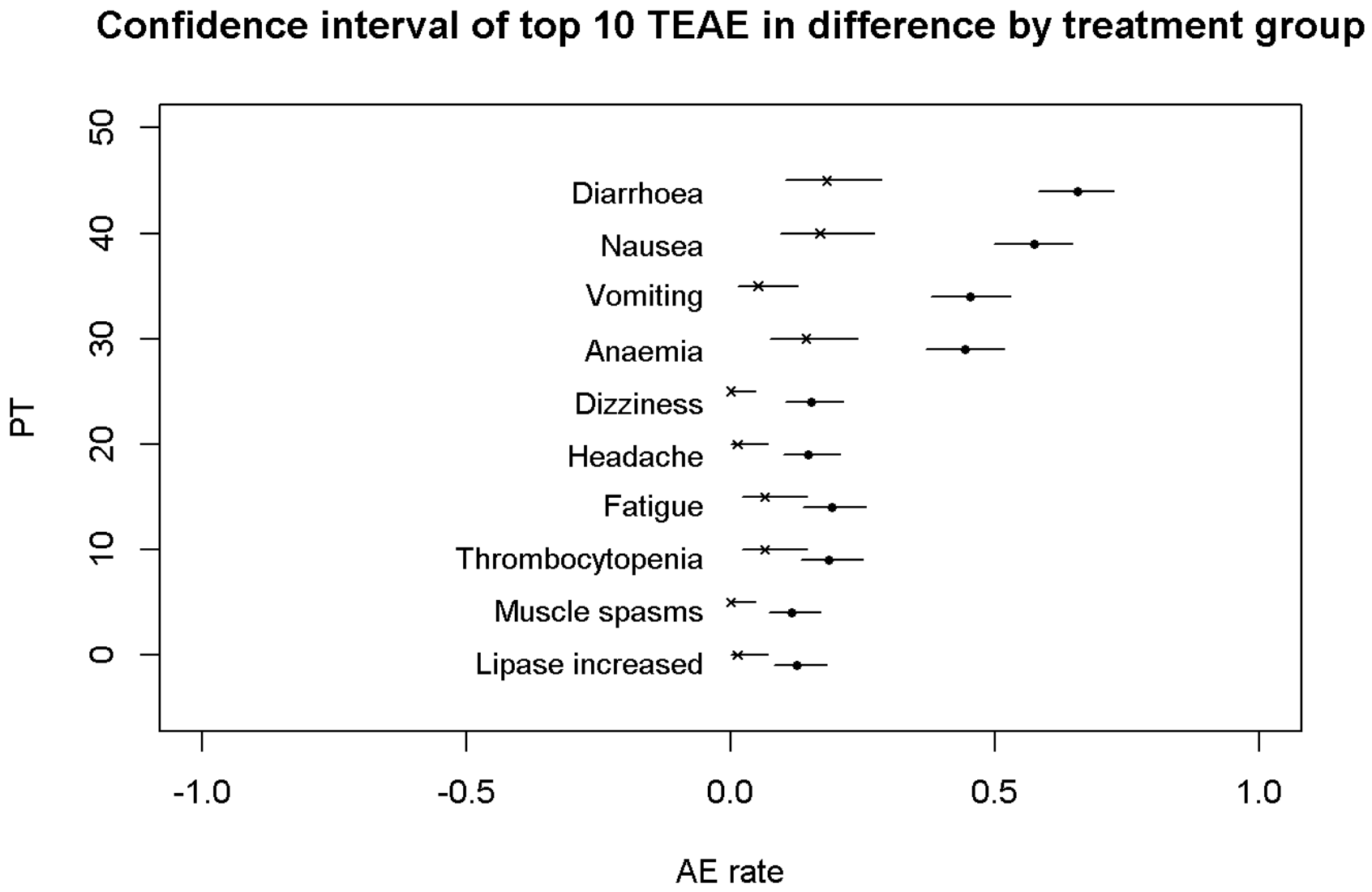
Issues for highlighting adverse events in clinical study report

- Reported AEs can be a mix of signal and noise due to the large number of AE types
  - Many AE types are possibly correlated within the body system
- Under discussion may overlook potential safety signal
- Simple inclusion of AEs may introduce noise
  - Nominal P-values can lead to false positive claims
  - False positive findings can equally mislead doctors and patients

Prototype Example of Data:
for illustrating the methods only; data modified for product blinding

- Pooled safety data from multiple trials for the same indication
  - Coded in MedDRA with SOC and Preferred terms
  - Caution on study and disease stage effect
- Analysis data included
  - N = 325 subjects
  - Two treatment groups (t or c)
  - 26 reported SOC, and 561 PT
    - Each subject may have 0, 1, or more than 1 reported AEs

Confidence Intervals of top 10 AEs : by preferred term



Use, Issue, and the Problem Definition

- The plots show relative sizes of AE rates
  - Non-overlapping confidence interval may suggest “significant” difference
- An ad hoc selection would be to highlight top 10 (or with rate difference exceeding some threshold, e.g., 5%), while including all remaining AEs in the tables without further editorial discussion
- Issues
  - The confidence interval approach lacks of multiplicity adjustment, resulting false positive findings from ad hoc interpretation
  - The ad hoc choice of threshold may have unintended impact
  - Potential correlation of AEs within the same SOC may not be properly accounted
- Problem definition
  - Objective selection of AEs that show different profiles between treatment groups
    - Measure for the effectiveness of the method: validation with training and testing data sets

General Model and MCMC estimation

Let $G = \{(SOC_b, PT_j) : b = 1, \cdots, B, j = 1, \cdots, k_b\}$ represent the select or reported MeDRA SOC and PT terms from a study (one trial or integrated safety adverse event data set). $Z = (Z_1, \cdots, Z_K)$ is a $Y = \prod_{k=1}^{K}\{0, 1\}$-valued random variable, representing a subject's observed adverse events. Let X be a $U = \{0, 1\}$-valued random variable, representing a subject's received treatment, either control or treatment group.

We consider a model $T_\theta : U \to Y$ as the random generator indexed by unknown θ, which is often high dimensional, so that $T_\theta(X)$ is equal to Z in distribution. Suppose we have sample $(X_i, Z_i), i = 1, \cdots, n$. Consider the joint distribution of $(\theta, Z_1, \cdots, Z_n)$ and the posterior distribution of θ given $(X_i, Z_i), i = 1, \cdots, n$, $\hat{\theta}$. The mean square loss function would be

$$\begin{aligned} Loss &= E|Z - ET_\theta(X)|^2 \\ &\approx \frac{1}{n}\sum_{i=1}^{n}|Z_i - ET_\theta(X_i)|^2, \end{aligned}$$

with θ evaluated through its MCMC samples.

Three Stages BAYESIAN HIERARCHICAL MODELING

Xia et al *Journal of Biopharmaceutical Statistics*, 21: 1006–1029, 2011

$$P(Z(SOC_b, PT_j) = 1) = \begin{cases} \frac{e^{\gamma_{bj}}}{1+e^{\gamma_{bj}}} & x = c, j = 1, \cdots, k_b \\ \frac{e^{\gamma_{bj}+\theta_{bj}}}{1+e^{\gamma_{bj}+\theta_{bj}}} & x = t, j = 1, \cdots, k_b \end{cases}$$

Note that we have

$$ET_{\gamma,\theta,\mu_\gamma,\sigma_\gamma,\mu_\theta,\sigma_\theta}(x)_{b,j} = 1(x = c)\frac{e^{\gamma_{bj}}}{1 + e^{\gamma_{bj}}} + 1(x = t)\frac{e^{\gamma_{bj}+\theta_{bj}}}{1 + e^{\gamma_{bj}+\theta_{bj}}}.$$

1. $\gamma_{bj}, j = 1, \cdots, k_b; b = 1, \cdots, B$; $\theta_{bj}, j = 1, \cdots, k_b; b = 1, \cdots, B$. These are from SOC population. For each b, they are independent and identically distributed among j's, with normal distribution with parameters in the following stage.

2. $\mu_{\gamma b}, \sigma_{\gamma b}; \mu_{\theta b}, \sigma_{\theta b}, b = 1, \cdots, B$. These are from patient population. For each parameter, they are independent and identically distributed among b's, with normal and gamma distributions with parameters in the following stage.

3. $\mu_{\gamma 0}, \tau_{\gamma 0}; \mu_{\theta 0}, \tau_{\theta 0}$. They are given with fixed normal and gamma distributions.

Bayesian Model with Ising Latent Variable

McEvoy et al Biometrics 69, 661–672, 2013

$$
\begin{aligned}
& P(Z_k = 1) \\
= & \begin{cases} \pi_k^1 & \gamma_k = 1 \\ I(x=1)\pi_k^1 + I(x=0)\pi_k^0 & \gamma_k = 0 \end{cases} \\
= & \begin{cases} \pi_k^1 & \gamma_k = 1 \text{ or } \gamma_k = 0, x = 1 \\ \pi_k^0 & \gamma_k = 0 \text{ and } x = 0 \end{cases}
\end{aligned}
$$

for $k = 1, \cdots, K$. Thus, the distribution of Z is determined or generated. Note that we have

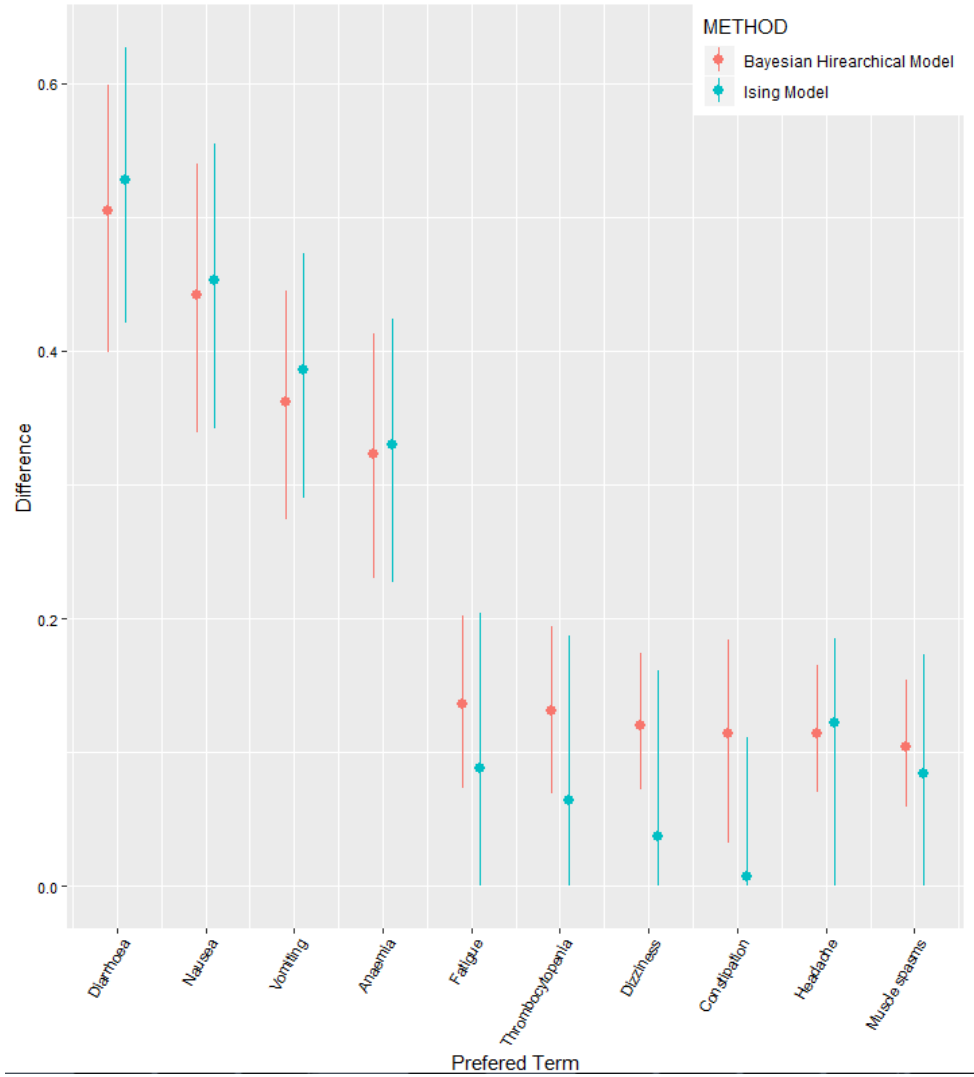
$$ET_{\nu,\pi}(x)_k = \pi_k^1[\gamma_k + (1-\gamma_k)x] + \pi_k^0(1-\gamma_k)(1-x).$$

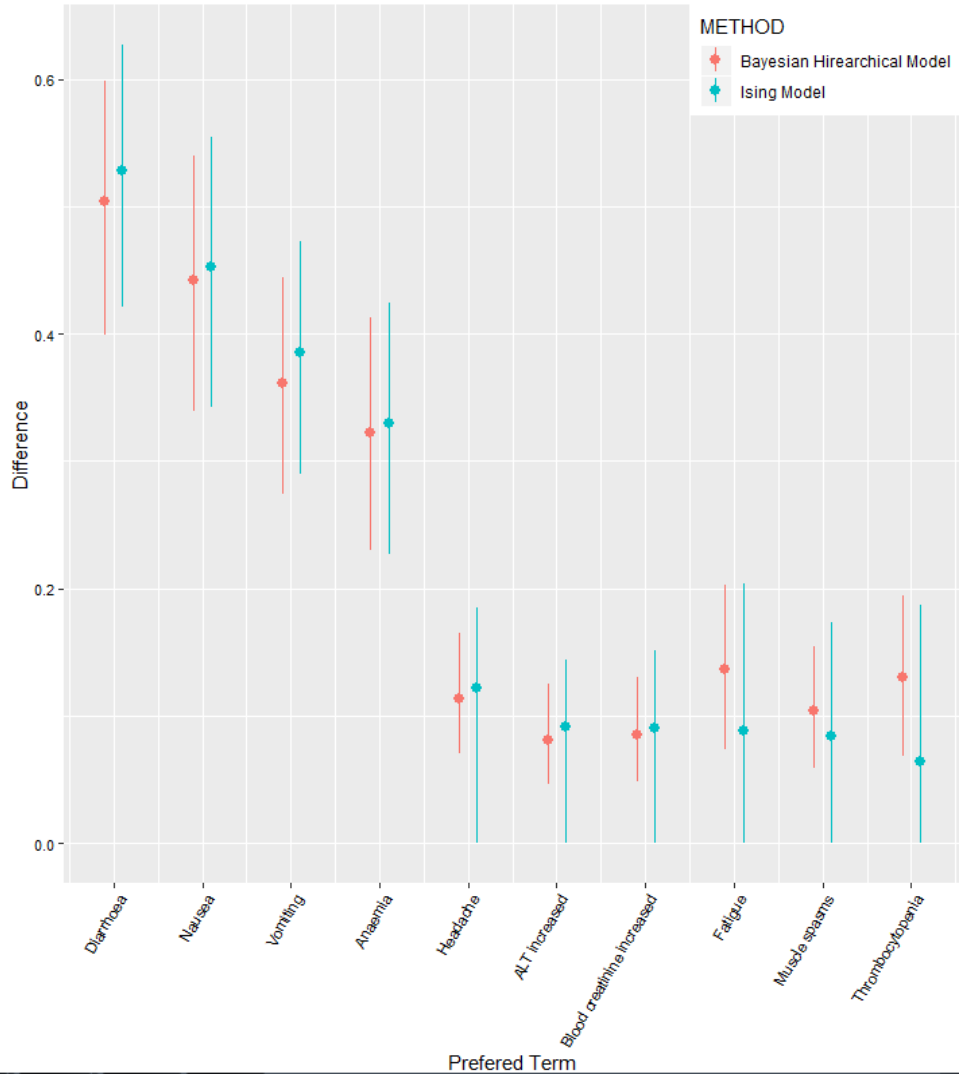
1. $\alpha_k = \alpha_k^i = 0.25$ and $\beta_k = \beta_k^i = 0.75$ for $i = 0, 1$.
2. $\rho_k = 1$ and $\theta = 0.2$
3. $\pi_k^1 \sim Beta(\alpha_k^1, \beta_k^1); \pi_k^0 \sim Beta(\alpha_k^0, \beta_k^0)$ for $k = 1, \cdots, K$
4. $\gamma = (\gamma_1, \cdots, \gamma_K)$ follows an Ising model with density function $f(\gamma|\theta, \rho) \propto H(\gamma; \rho, \theta) = \exp(\sum_{k=1}^K \rho_k \gamma_k + \theta \sum_{k=1}^K \sum_{j \in D_k} I(\gamma_k = \gamma_j))$, where $\rho = (\rho_1, \cdots, \rho_K)$.

Splitting the Prototype Example of Data:

- Data included
  - N = 325 subjects
    - 80% training; 20% testing
  - Two treatment groups (t or c)
  - 26 reported SOC, and 561 PT
    - Retain the same categories between training and testing data sets, and allow zero count
- Use training data MCMC samples to evaluate MSE in testing data for prediction accuracy

Top 10 AEs
Selected by Three Stages Model (left) and Ising Prior Model (right)





Mean Square Errors

	Three Stages Model	Ising Model
Training data	12.1	19.1
Testing data	15.1	17.1

$$
\begin{aligned}
Loss &= E|Z - ET_\theta(X)|^2 \\
&\approx \frac{1}{n}\sum_{i=1}^{n}|Z_i - ET_\theta(X_i)|^2
\end{aligned}
$$

Pros and Cons

Method	Pros	Cons
Confidence interval	• Help reader understand incidence and variability • Visual contrast between groups • Easy implementation	• Increase false alert due to lack of multiplicity control • Manual comparison for overlapping CIs
Bayesian hierarchical	• Easy flag for AE difference • Avoid multiplicity discussion • Reasonable cross validation	• Limited account for AEs correlation
Ising model	• Easy flag for AE difference • Avoid multiplicity discussion	• Difficulty in choosing hyperparameters • May have poor cross validation

Discussion

- Three stages Bayesian model appears to work well overall
  - Avoid multiplicity issue
  - Reasonable cross validation
  - Easy implementation via RJAGS
  - Consistent with simple confidence intervals approach
- Recommendation can be reinforced by application to additional study data