**Background**

- Blinded AE monitoring during conduct of Biosimilar trial
- Historical information about AE terms of interest from originator

- Put AE on trial in context with historical data
- AE rate unexpectedly low/high?
- Further investigation required?

**Prior information**

- Probability $p$ that patient experiences AE
- Originator trial with $N_H$ patients, $N_H Y_j$ experienced event
- Weight $y$ for prior information

$$ p = \text{Beta}(\gamma N_H Y_j, \gamma N_H (1 - Y_j)) $$

- Choose weight s.t. prior is informative especially early on
- Could consider formal meta-analysis on historical trials for $p$ and resulting prior effective sample size

**Data updating**

- Observed data $X_t$ (at time point $t$)
- Indicator for patient $j$ with AE: $Y_j$
- $Y_j = 1$: The patient experienced this AE at least once
- Assume same probability $p$ for each of $N_t$ patients
- Binomial likelihood for $Y_t = \sum_{j=1}^{N_t} Y_j$

**Posterior distribution**

- Conjugate Beta distribution
- Posterior is Beta as well

$$ p(Y_t) = Y_t \text{Beta}(\gamma N_H Y_j + y, \gamma N_H (1 - Y_j) + N_t - Y_t) $$

**Monitoring**

- IF AE rate throughout ongoing trial higher than expected from historical data, posterior will describe increasingly higher AE rate converging to new AE rate

- Example:
  - At every time point 100 additional patients
  - At every time point, 20 additional patients with AE
  - 10 - effective data 100 patients, 10 with AE

**Decision criteria**

- Warning or Alert if posterior AE rate greater than a predefined threshold with a certain trigger probability
- Warning
- Alert

- Otherwise consider “safe”
- Thresholds and trigger probabilities tbd with medical input
- Trade-off between too many false alarms and risk of overlooking signal

**Choice of parameters**

- Simulation example
  - Historical data with $p_H$ weighted size
  - m monitoring time points in new phase III trial
  - Assume medical input was: safe if “true” RR in new trial is $\alpha_A$
  - m monitoring if RR=1

- Warning or Alert if posterior AE rate greater than $\alpha_W$

**Discussion**

Easy to motivate to medical/drug safety

**Applicability**

- Can use for single arm trials in general
- Consider pooled blinded analysis for superiority trial to combine historical information on comparator and earlier phase information on new drug

**Summary table**

- Comparison of 95% credible interval from posterior distribution and 95% Wilson score confidence interval

- Error rate at end of comparator trial overestimates AE rate while trial ongoing
- Time at risk not considered/not controlled between trials
- Simple proportions of patients with an AE the appropriate measurement?
- Time-to-event information on AE available on own substance from earlier development phases but not on comparator

- AE rate at end of comparator trial overestimates AE rate while trial ongoing unless AE occurs early if it occurs at all

**References**