Analysis of Adverse Events using Literature Data: a Simulation Study

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OBJECTIVES

- To explore the value of meta analysis of adverse event (AE) and model properties, specifically, evaluate:
  - Ability to estimate treatment effects precisely
  - Consequence of mixing studies of different sample size (N)
  - Usefulness of standard modeling diagnostics tools
- **Methodology**
  - Simulate data that closely resemble outcome under clinical settings
  - Use glme (Splus) or glmer (R)

BACKGROUND

- Clinical outcome expressed as a proportion, such as %AE's or %responders, may be treated as a continuous variable and modeled using standard mixed effects algorithms
- Lack of fit will likely occur if proportions are close to the boundaries 0% or 100%. A Logit transformation (on proportions) in some instances helps but dose not resolve the problem completely
- Instead, proportions are converted to a binary outcome and are modeled as such
- Similar functions and model definition are available in Splus or R, producing similar results

MODEL

- Using proportions data together with sample size, the number of events is constructed and is dealt with as a binomial variable
- A binomial model estimates the probability of an event (p) as a function of influential variables (X), as expressed in equation (1)
- The covariate vector X can be any combination of discrete, categorical, factor and continuous variables

$$\log\left(\frac{p_{ij}}{1-p_{ij}}\right) = \sum_{k=1}^{m} X_{ijk}.\beta_{ijk} + \eta_j \qquad (1)$$

X_{ijk} is a vector of k covariate values observed in the *ith* arm of the *jth* study

β_{ijk} is a vector of parameter coefficients to be estimated

$\eta_j \sim N(0,\sigma^2)$ is study random effect

EXAMPLE

- Outcome from 40 clinical trials comparing a hypothetical active treatment vs. placebo, N=100 per arm were simulated
  - Assumed two groups of clinical trials, A and B (20 studies each)
    - A: with proportion of AE's higher than placebo by 30%
    - B: with proportion of AE's higher than placebo by 10%
  - Assumed various sample size ratios of studies A and B to total sample size: 99.7%, 99.4%, 99%, 98.5%, 98%, 97%, 96%, 95%, 90%, 80%, 70%, 60%, 50%, 40%, 30%, 20%, 10%, 5%, 4%, 3%, 2%, 1.5%, 1%, 0.6%, 0.3%
  - For example a ratio of 10% means: sample size of group A studies was 10% of total sample size, see Figure (1)
  - Under each sample size scenario a glme (Splus) or glmer (R) was fitted
- Equation (1) is now reduced to

$$\log\left(\frac{p_{ij}}{1-p_{ij}}\right) = \alpha + \beta + \eta_j$$

α: intercept

β: Treatment effect

Inter-study variability ~$N(0,\sigma 2)$, σ = 0.2, representing CV of 20%

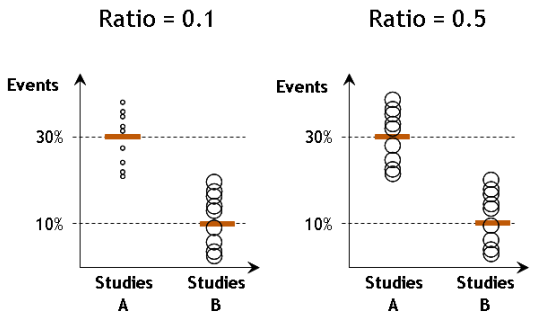

Figure 1: Contribution of Groups A and B studies to total Sample Size

RESULTS

- Under each sample size scenario, treatment effects (estimated proportions of events) were outputted. Figure (2) plots the estimates against sample size ratio
- Because the contribution to the likelihood is inherently proportional to sample size, resulting in a proportional effect on model estimates, and independent of the effect of random effects
- Estimated random effects, residuals and their respective variances were in close agreement to the true values
- Figure 2 illustrates that when group A or B dominates sample size, estimated treatment effect is close to 0.3 or 0.1, respectively, despite equal number of studies for each group
- Similar findings were obtained when inter-trial variability is increased, however, study sample size required is to increase to achieve unbiased estimates
- Various other simulations with designs similar to clinical trial settings produced similar conclusions
- Use of observed vs. fitted proportions carries the risk of concluding lack of fit, especially when for the case of large number of studies with small N, typical of early Phase II trials
- Instead, diagnostics should be based on residuals, e.g. Pearson residuals or adjusted deviance residuals.
- Lack of subject level information limits the scope of meta data analysis of literature data [1,2], however, for binary outcome, reconstruction of subject level response more than compensates this limitation, rendering this type of analysis highly informative

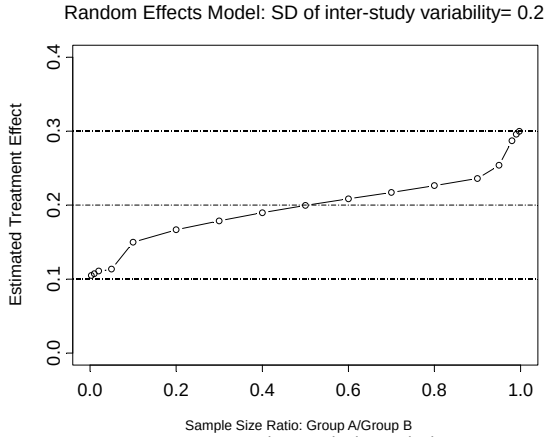

Figure 2: Estimated Treatment effect vs. Sample Size Ratio

- The findings of the meta analyses from literature data in cancer trials and from the osteoarthritis trials [3] where consistent with those of this simulation work.

CONCLUSIONS

- No ad hoc weighting by sample size is necessary when response is expressed as a proportion and analyzed as binomial
- More importantly, proportion data when converted to a binomial outcome essentially re-constructs the observed response at the patient level.
- The pooled trials thus retain original sample size and significantly increase model precision and statistical power
- This is particularly useful when investigating rare events from a large number of small studies, as in early phase cancer trials.

REFERENCES

[1] F. Ezzet, F., P. Ravva, T. Tensfeldt. Model-Based Literature Meta-Analysis: Virtues and Limitations, ACoP, Tucson, Arizona, March, 2008, (http://tucson2008.go-acop.org/pdfs/17-Ezzet_FINAL.pdf)
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[3] F. Ezzet, K. Prins, M. Boucher. PAGE 19 (2010) Abstr 1771 [www.page-meeting.org/?abstract=1771]