Exposure-Response Analysis of Adverse Events in Clinical Trials Using Zero-Inflated Poisson Modeling With NONMEM®

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Introduction

Count data, typically characterized by the number of occurrences of an event during a specified time interval, often arises in clinical trials and are usually characterized and modeled by Poisson distribution. Often times, such kind of data is associated with adverse events. However, some adverse events may only be observed in a small portion of the study subjects, resulting in excessive zeros in the data. Exposure-response modeling of such data allows for a better understanding of the relationships between drug exposure and event rate and helps identify potential risk factors that make subjects prone to certain adverse events.

Objectives

The objectives of the analysis were:

- to model event rate of an adverse event following administration of a new investigational drug;
- to assess the potential relationships between the occurrence of the adverse event and the extent of drug exposure;
- and to identify potential risk factors that influence the occurrence of the adverse event.

Methods

- Zero-inflated Poisson (ZIP) regression models [1] were explored and developed using NONMEM® to characterize the zero-rich count data for the adverse event.
- Regular Poisson and Negative Binomial regression were also fitted to the data; and the results were compared to that from the ZIP model.
- Covariate modeling to identify potential risk factors: drug exposure, demographic variables, and other relevant variables were examined on both logistic and truncated Poisson components of the ZIP
- The ZIP model was evaluated using marginal calibration diagram [2] and used to simulate exposure-adverse event response curves and placebo effect.

Table 1. Model Development

Run	OFV	ΔOFV	MIN	COV	REF	Model
Base Model						
ZIP100	1542					
Full Model						With all clinically relevant covariates
ZIP101	1373	-169	y	y	ZIP100	Linear exposure-response relationship on Poisson part
ZIP102	1339	-34	y	y	ZIP101	Emax-type exposure-response on Poisson part
ZIP103	1344	-29	y	n	ZIP101	Emax-type exposure-response on logistic part
ZIP104	1338	-35	y	y	ZIP101	Emax-type exposure-response on both logistic and Poisson
Reduced Model						
ZIP105	1345	6	y	y	ZIP102	Remove 6 covariates with SE% > 100%

Zero-Inflated Poisson Model

$$P(Y=0) = \phi + (1-\phi)e^{-\lambda}$$

$$P((Y=y) = (1-\phi)\frac{e^{-\lambda}\lambda^{y}}{y!} \qquad y = 1,2,3\cdots$$

The logit of parameter, ϕ, and log event rate (λ) can be modeled as a function of covariates:

$$\log it(\phi_{ij}) = f(x_{ij})$$

$$\log \lambda_{ij} = g(w_{ij})$$

A linear function $(\beta \bullet Exposure_i)$ or a Emax-type function $(\frac{\beta \bullet Exposure_i}{EC50 + Exposure_i})$ can be used for exposure to the drug. Linear functions were used for the other covariates.

Results

Figure 1. Comparison of Model Performance of Poisson Model, Negative Binomial Model, and Zero-Inflated Poisson Model

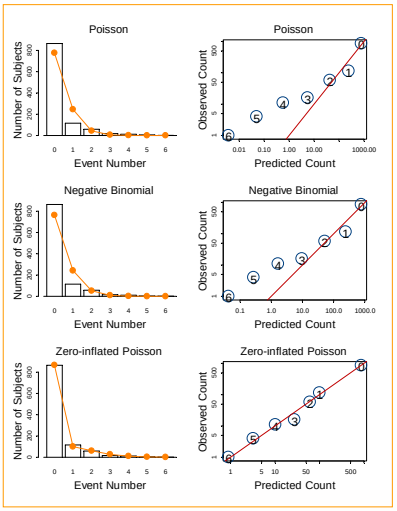


Figure 2. Identification of Functional Form of Exposure Measures (Logistic Part)

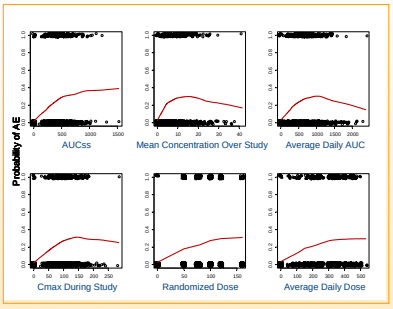


Figure 3. Identification of Functional Form of Exposure Measures (Poisson Part)

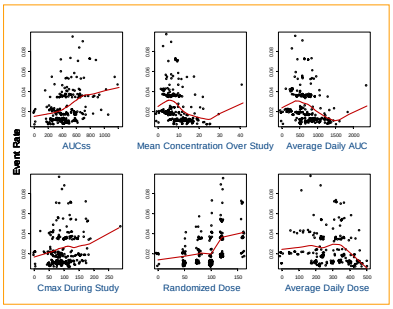
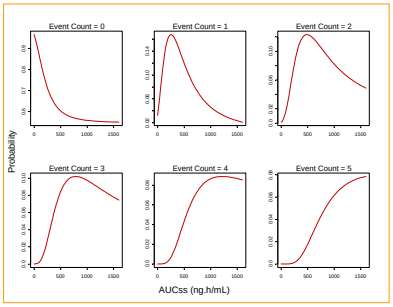


Figure 4. Simulated Exposure-Response Curve



Summary

- ZIP models adequately characterized the distribution of the adverse event, while Poisson and Negative Binomial models tended to underestimate the event rate.
- Drug exposure was identified as significant risk factor. An Emax model best described the relationship between the occurrence of the adverse event and drug exposure.
- Certain demographic variables, such as sex and body weight, were also identified as risk factors.
- The simulation suggested that higher the drug exposure, the more episodes of the adverse event a subject would be expected to experience.
- Zero-inflated Poisson regression can be implemented in NONMEM® and is a useful tool to model the occurrence of an adverse event, where no instance of the adverse event were reported in majority of subjects.

Reference

1. Johnson NL, Kotz S, Kemp AW. Univariate Discrete Distributions, 2nd edn. Wiley: New York, 1992.

2. Czado, C., Gneiting, T., Held, L. (2007) Predictive Model Assessment for Count Data. University of Washington Department of Statistics Technical Report no. 518.