Adjusted Analysis of Latent Adverse Events in Clinical Trials with Censored Follow-up

Mei Yong
University Hospital Duesseldorf, Department of Statistics in Medicine,
University Street 1, Building 23.02, Level 03,
40225 Duesseldorf, Germany
yong@uni-duesseldorf.de

Jochen Mau
University Hospital Duesseldorf, Department of Statistics in Medicine,
University Street 1, Building 23.02, Level 03,
40225 Duesseldorf, Germany

In long-term follow-up studies, irregular recall visits and unavoidable drop-outs from follow-up may complicate the assessment of long-term efficacy and safety: The occurrence rates of events depend not only on the exposure times but also on the frequencies of visits which may increase the chance to detect an event. Hence, the exposure times and frequencies of inspections should be taken into account in the analysis of complications in a similar way as it is done in efficacy analyses that involve survival data techniques. The method is illustrated with the safety analysis in a clinical trial of dental implants.

In a randomized multicenter study, 2 intramobile cylinder (2 IMZ) and 4 titanium-plasma sprayed screw (4 TPS) dental implants were compared in 313 totally edentulous mandibles. According to protocol, the implants should be examined every 6 months during subsequent follow-up after placement of prosthesis. It should be taken attention, that 4 pieces of implants were used in each patient of the TPS group but only 2 in each patient of the IMZ group, which may lead to an increased chance of occurrence of complication for TPS group patients. Because of different exposure time, different frequency of inspection and different number of implants in the two group of patients, considerable potential of confounding can be introduced in the analysis of complications. Hence, an adjustment was made for the number of implants within a system and the number of recall inspections of a patient: an exposure concept, analogous to the total-time-on-test concept, used the total number of implants and of implant inspections. The comparison is hence adjusted for the differences in numbers of recall visits due to heterogeneous lengths of observation. The complication occurrence rate of this statistical estimator corresponds to the common hazard estimator of an exponential failure time distribution.

More formally, assume an underlying Poisson process to represent the counts of complications that can be detected on the potentially infinite set {1, 2, …} of inspections of any particular implant j within any particular patients i; then

$$\text{Prob}\{N_{ijk} = n\} = \exp(k\lambda_{ij})(k\lambda_{ij})^n/n!$$

is the probability to see exactly n complications during k inspections of implant j of patient i, when $\lambda_{ij} > 0$ is the rate of occurrence of complications per inspection of an implant, and

$$E(N_{ijk}) = k\lambda_{ij},\ j = 1, \ldots, m_i,\ i = 1, \ldots, n.$$

The finite calender period of observation of patient i implies a (random) number l_{ij} of conducted inspections at which complications can be seen on implant j, hence

$$L = \sum_{i=1,\ ¼\ n} \sum_{j=1,\ ¼\ mi} l_{ij}$$

is the total number of inspections of which complications may be seen and

$$N = \sum_{i=1,\ ¼\ n} \sum_{j=1,\ ¼\ mi} N_{ij} l_{ij}$$

the total number of complications counted across all patients, implants, and implant inspections. Then

$$\lambda^{est} = N/L$$

is an estimator of common rate λ, $\lambda = \lambda_{ij}$, $j = 1, \ldots, m_i$, $i = 1, \ldots, n$.

With the variance, $V(\lambda^{est}) = N/L^2$, one obtains an approximate $(1-\alpha)$-confidence interval of λ from the Gaussian distribution. For a comparison of λ's in two populations pertaining to two independent samples of patients, one then obtains a test statistic as

$$(\lambda^{est}{}_1 - \lambda^{est}{}_2) / \sqrt{(N_1/L_1{}^2 + N_2/L_2{}^2)}$$

which is to be referred to the standard Gaussian distribution as well.

The results were then given in *percent per implant inspection* (%*pii*) with 95%-confidence interval (95% CI).

After placement of prosthesis, there were 358 occurrences of complications documented in 3626 total implant inspections in IMZ group and 910 complications in 6821 total implant inspections in TPS group. Following is the comparison of complications and their adjusted complication rates between two groups.

Table 1. Occurrence of complications after placement of prosthesis

	Assigned Treatment		Test	
	2-IMZ	4-TPS	*z*	*P*
Infection	3.3% (2.7-3.9%)	7.4% (6.8-8.1%)	-9.29	<0.0001
Pain	0.3% (0.1-0.5%)	0.3% (0.2-0.5%)	-0.55	0.58
Position change	0.01% (0-0.05%)	0.04% (0-0.1%)	-0.94	0.35
Recession	0.6% (0.3-0.8%)	2.7% (2.3-3.1%)	-9.08	<0.0001
Fracture of implants	0.2% (0.03-0.3%)	0.01% (0-0.03%)	2.31	0.02
Other complications	5.6% (4.8-6.3%)	2.8% (2.4-3.2%)	6.28	<0.0001
Total number of implant inspections	3626	6821		