Linear Categorical Marginal Modeling of Solicited Symptoms in Vaccine Clinical Trials

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Introduction

In vaccine clinical trials the safety of a new vaccine is usually compared to a reference in terms of

- solicited symptoms
- unsolicited symptoms

Solicited symptoms are recorded via standardized diary cards by the subject daily during x days after vaccination and are often categorized for ease of collection, e.g.

Pain (at injection site)	
0	Absent
1	Minor reaction to touch
2	Cries/protests on touch
3	Cries when limb is moved/spontaneously painful

Example: evaluation of a new meningoccoccal vaccine against a control vaccine (Phase III randomized trial). Results for pain:

	Control (N=499)		Active (N=1381)		Control - Active	95% CI		*p*-value	
Intensity	n	%	n	%	%	LL	UL	Raw	B-H
				Day 1					
1, 2 or 3	333	66.7	929	67.3	-0.54	-5.8	4.39	0.824	1.000
2 or 3	143	28.7	300	21.7	6.93	2.25	12.02	0.002	0.021
3	33	6.6	31	2.2	4.37	1.83	7.63	<0.001	0.001
				Day 2					
1, 2 or 3	252	50.5	613	44.4	6.11	1	11.41	0.021	0.169
2 or 3	93	18.6	153	11.1	7.56	3.55	12.11	<0.001	0.001
3	14	2.8	14	1	1.79	-0.03	4.42	0.008	0.075
				Day 3					
1, 2 or 3	116	23.2	264	19.1	4.13	-0.31	9.05	0.051	0.358
2 or 3	25	5	43	3.1	1.9	-0.53	5.08	0.068	0.407
3	2	0.4	7	0.5	-0.11	-2.22	1.74	1.000	1.000
				Day 4					
1, 2 or 3	49	9.8	102	7.4	2.43	-0.8	6.35	0.102	0.509
2 or 3	10	2	14	1	0.99	-0.68	3.49	0.104	0.509
3	2	0.4	4	0.3	0.11	-0.98	2.08	0.659	1.000

Different ways to deal with these many comparisons

$\rightarrow$ when comparing 2 vaccines, potentially many potentially correlated differences to test

Different options :

- use multiplicity corrections (Bonferroni(-Holms), FDR, ...)
- adapt endpoint (symptom occuring any day)
- use models taking into account repeated measures $\rightarrow$ LCMMs

LCMMs = Linear Categorical Marginal Models

Modeling differences in marginal proportions (1 rep. factor)

1 rep. factor : T = Time.
Only one intensity of symptom S (e.g., any intensity: 1, 2, or 3).

$\pi^{G S_1 S_2 S_3 S_4}_{g\ s_1\ s_2\ s_3\ s_4}$ = proportion of subjects in group $G = g$ with symptom $S_i = s_i$ on day i ($S_i = 1$ if the symptom occurred on day i and $S_i = 0$ if the symptom did not occur on day i)

$\pi^{S G|T}_{s\ g\ t}$ = prop of subjects in group $G{=}g$ with $S{=}s$ given $T{=}t$.
These are marginal proportions, e.g., $\pi^{S G|T}_{s\ g\ 1} = \pi^{G S_1 S_2 S_3 S_4}_{g\ s\ + + +}$

$\pi^{S|G T}_{s\ g\ t} = \frac{\pi^{S G|T}_{s\ g\ t}}{\pi^{S|T}_{s\ t}}$ = conditional probability $S = s\,|G = g, T = t$.

Modeling differences in marginal proportions (1 rep. factor)

$\delta_t^T = \pi_{1\,1\,t}^{S|GT} - \pi_{1\,2\,t}^{S|GT}$: differences in conditional probabilities for active and control group at time t.
can be estimated by different models:

- the *no difference model* : $\delta_t^T = 0 \qquad \forall t$
- the *constant difference model* : $\delta_t^T = \alpha \qquad \forall t$
- the *varying effect model* : $\delta_t^T = \alpha + \beta_t \qquad \forall t$

models are linear in these conditional probabilities
$\rightarrow$ *Linear Categorical Marginal Models (LCMMs)*

LCMM : Linear Categorical Marginal Models

Let π the vector of all $\pi^{G S_1 S_2 S_3 S_4}_{g\ s_1\ s_2\ s_3\ s_4}$s. The vector of marginal proportions of interest are a linear combination of the elements of π and can be written as

$$\mathbf{M}\pi$$

Let δ be the vector of δ_t^T. δ can be obtained from $\mathbf{M}\pi$ by:

$$\delta = \delta(\mathbf{M}\pi) = \mathbf{C}' \exp \mathbf{B}' \log \mathbf{A}'\mathbf{M}\pi$$

A linear model for δ, i.e., a LCMM, can then be denoted as

$$\delta(\mathbf{M}\pi) = \mathbf{X}\beta \tag{1}$$

or equivalently (with appropriate $\mathbf{U}$)

$$\mathbf{U}'\delta(\mathbf{M}\pi) = \mathbf{0} \tag{2}$$

$\rightarrow$ 2 different estimation procedures :
- Weighted Least Squares (WLS: Grizzle, Starmer & Koch, 1969)
- Maximum Likelihood (ML: Lang & Agresti, 1994).

ML : maximize the multinomial log likelihood $L(\pi|\mathbf{n})$ under constraint (2). Solution is a stationary point of the Lagrangian expression

$$L(\pi|\mathbf{n}) - \lambda'\delta(\mathbf{M}\pi)$$

with λ vector of Lagrange multipliers (see, Bergsma, Croon, & Hagenaars, 2009).

Goodness of fit statistic :

$$G^2 = -2N \sum_i p_i \log \frac{\hat{\pi}_i}{p_i}$$

Application to the example

When considering any intensity only:

Table : *ML Estimates of different LCMMs for the solicited symptoms observed during the 4-day post vacc. period.*

	Model Fit				Expected difference Control - Active		Model-based *p*-value	
Model	G^2	df	*p*-value	Day	Diff	se	Unadj.	B-H
No diff.	8.46	4	0.076	1, ..,4	0			
Constant diff.	6.16	3	0.106	1,...,4	1.95	1.32	0.140	
Varying	0.00	0	1.000	1	-0.54	2.46	0.827	0.827
effect		-		2	6.11	2.61	0.019	0.076
		-		3	4.13	2.17	0.057	0.171
		-		4	2.43	1.51	0.106	0.212

Modeling differences in marginal proportions (2 rep. factors)

$\delta^{TR}_{t\,r} = \pi^{R|GT}_{r\,1\,t} - \pi^{R|GT}_{r\,2\,t}$: difference in marginal proportions between active and control group at time t for intensity level of at least r can be estimated by different models:

- *no difference* : $\delta^{TR}_{t\,r} = 0 \quad \forall t, r$
- *constant difference* : $\delta^{TR}_{t\,r} = \alpha \quad \forall t, r$
- *cst difference by intensity* : $\delta^{TR}_{t\,r} = \alpha + \beta^{R}_{r} \quad \forall t, r$
- *independent intensity by time* : $\delta^{TR}_{t\,r} = \alpha + \beta^{T}_{t} + \beta^{R}_{r} \quad \forall t, r$
- *saturated* : $\delta^{TR}_{t\,r} = \alpha + \beta^{T}_{t} + \beta^{R}_{r} + \beta^{TR}_{t\,r} \quad \forall t, r$

Application to the example

When considering any, $\geq$grade 2, and $\geq$grade 3 intensity levels simultaneously during the 4 days follow up period:

Table : *Fit of different marginal models on pain of several intensities (4-day post vaccination period)*

	Model Fit		
Model	G^2	df	p-value
No difference	33.8	12	<0.001
Constant difference	32.5	11	<0.001
Constant difference by intensity	29.9	9	<0.001
Independent intensity by time	16.1	6	0.013
Saturated	0.0	0	1.000

Table : *Differences in % reporting pain post vacc.*

	Control - Active				
		95% CI		*p*-value	
Intensity	%	LL	UL	Raw	B-H
		Day 1			
1, 2 or 3	-0.54	-5.8	4.39	0.824	1.000
2 or 3	6.93	2.25	12.02	0.002	**0.021**
3	4.37	1.83	7.63	<0.001	**0.001**
		Day 2			
All	6.11	1	11.41	0.021	0.169
2 or 3	7.56	3.55	12.11	<0.001	**0.001**
3	1.79	-0.03	4.42	0.008	0.075
		Day 3			
1, 2 or 3	4.13	-0.31	9.05	0.051	0.358
2 or 3	1.9	-0.53	5.08	0.068	0.407
3	-0.11	-2.22	1.74	1.000	1.000
		Day 4			
1, 2 or 3	2.43	-0.8	6.35	0.102	0.509
2 or 3	0.99	-0.68	3.49	0.104	0.509
3	0.11	-0.98	2.08	0.659	1.000

Any : none sign
≥ 2 : sign d1 and d2
≥ 3 : sign d1

Conclusions

Potentialities in use of LCMMs

- repeated measures taken into account: allows to evaluate structure of differences via correct overal statistical tests
- linear models

Limitations (ML estimation)

- missing data not yet handled
- not available in standard statistical software

Selected references :

Bersgma, W.P., Aris, E. M. D., & Tibaldi, F. (2012). Linear categorical marginal modeling of solicited symptoms in vaccine clinical trials. *Journal of Biopharmaceutical Statistics*. Forthcoming.

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Grizzle, J.E., Starmer, C.F., & Koch, G.G. (1969). Analysis of categorical data by linear models. *Biometrics, 25,* 489-504.

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Annex 1

WLS is based on the the asymptotic covariance matrix of the sample value of $\delta(\mathbf{M}\pi)$. Using the delta method this leads to the WLS estimator

$$\tilde{\beta} = \left(\mathbf{X}' \left(\mathbf{J}\mathbf{M}\mathbf{D}_{\mathbf{p}}\mathbf{M}'\mathbf{J}'\right)^{-1}\mathbf{X}\right)^{-1}\mathbf{X}' \left(\mathbf{J}\mathbf{M}\mathbf{D}_{\mathbf{p}}\mathbf{M}'\mathbf{J}'\right)^{-1}\mathbf{J}\mathbf{M}\mathbf{p}.$$

where $\mathbf{J}$ is the Jacobian of δ, $\mathbf{p}$ is the vector of observed probabilities, and $\mathbf{D}_{\mathbf{p}}$ is the diagonal matrix with $\mathbf{p}$ on the main diagonal.

Annex 2

Comparison between ML and WLS when considering any, ≥grade 2, and ≥grade 3 intensity levels simultaneously during the 4 days FU period:

No difference model			Constant difference model			Constant difference model by intensity			Independent intensity & time effect model		
G^2	df	p-value	G^2	df	p-value	G^2	df	p-value	G^2	df	p-value
33.8	12	**<0.001**	32.5	11	**<0.001**	29.9	9	**<0.001**	16.1	6	**0.013**
W^2	df	p-value	W^2	df	p-value	W^2	df	p-value	W^2	df	p-value
27.6	12	**0.006**	27.5	11	**0.004**	26.4	9	**0.002**	15.4	6	**0.017**

Annex 3

Fit of different LCMMs (several intensities) 4-day post vacc. (ML)

Symptom	No difference model			Constant difference model			Constant difference model by intensity			Independent intensity & time effect model		
	G^2	df	p-value	G^2	df	p-value	G^2	df	p-value	G^2	df	p-value
Pain	33.8	12	<0.001	32.5	11	<0.001	29.9	9	<0.001	16.1	6	0.013
Redness	22.5	12	0.032	21.7	11	0.027	7.11	9	0.625	1.8	6	0.938
Irritability	15.3	12	0.221	15.4	11	0.166	10.75	9	0.293	7.6	6	0.269

Effect estimates of the constant difference by intensity models

		Control - Active					
		0 vs 1,2,3		0,1 vs 2,3		0,1,2 vs 3	
Symptoms	Day	Diff (%)	p-value	Diff (%)	p-value	Diff (%)	p-value
Redness	1,2,3,4	4.93	0.003	2.18	0.009	-0.17	0.124
Pain	1,2,3,4	1.22	0.325	1.59	0.025	0.814	0.041