MPS Medical and Pharmaceutical Statistics Research Unit

International Society for Clinical Biostatistics
Prague, August 2009

A combined score test for binary and ordinal endpoints from clinical trials

John Whitehead, Mike Branson and Susan Todd

Medical and Pharmaceutical Statistics Research Unit
Director: Professor John Whitehead
Tel: +44 1524 592350
Fax: +44 1524 592681
E-mail: j.whitehead@lancaster.ac.uk

MPS Research Unit
Department of Mathematics and Statistics
Fylde College
Lancaster University
Lancaster LA1 4YF, UK

The ICTUS trial in stroke

- Patients who have suffered acute stroke
- Randomised between citicoline and placebo
- Assessed at 90 days on
  - *Barthel index*
  - *modified Rankin score*
  - *NIHSS*
- Prognostic factors
  - *baseline NIHSS*
  - *time from stroke to treatment (≤ or > 12 hours)*
  - *age (≤ or > 70 years)*
  - *site of stoke (right or left side)*
  - *use of rTPA (yes or no)*

Methodological challenges

1. Combine the three stroke scales
    – *following Tilley et al., 1996*
2. Include up to three interim analyses
3. Adjust for the five prognostic factors
4. Adjust for treatment centre (around 60 of them)

The approach used by Tilley et al

Combine the three analyses using GEE
(based on an independence covariance structure: IEE)

That is, analyse as if the three scores were independent, but adjust the standard error of the treatment effect estimate using the sandwich estimator

- complicated to understand
- no associated sample size formula
- failed in test data set of 1000 patients with binary responses and adjustment for 60 centres
- SAS will only implement IEE for ordinal data

An alternative general approach

The score statistic Z_i is used to test $H_{0,i}$: $\theta_i = 0$, where $Z_i \sim N(\theta_i V_i, V_i)$ when information V_i is large and θ_i is small

Test H_0: $\theta_1 = \ldots = \theta_k = 0$ using $Z = Z_1 + \ldots + Z_k$

If $\theta_1 = \ldots = \theta_k = \theta$, then approximately

$$Z \sim N\left(\theta V, V + \sum_{i,j} C_{ij}\right)$$

where $V = V_1 + \ldots + V_k$ and $C_{ij} = \mathrm{cov}(Z_i, Z_j)$

It follows that, if

$$Z^* = \frac{ZV}{V + \sum_{i,j} C_{ij}} \quad \text{and} \quad V^* = \frac{V^2}{V + \sum_{i,j} C_{ij}}$$

then

$$Z^* \sim N\left(\theta V^*, V^*\right)$$

as required for sample size calculation and sequential analysis

What we need to use this is an expression for

$$C_{ij} = \text{cov}(Z_i, Z_j)$$

The binary case, no covariates

	E	C	Total
Success	S_E	S_C	$S_\bullet$
Failure	F_E	F_C	$F_\bullet$
Total	$n_{E\bullet}$	$n_{C\bullet}$	n

$$Z = \frac{n_{C\bullet}S_E - n_{E\bullet}S_C}{n} \quad \text{and} \quad V = \frac{n_{E\bullet}n_{C\bullet}S_\bullet F_\bullet}{n^3}$$

Covariance between Z_i and Z_j

For two such statistics, we have

$$C_{ij} = \operatorname{cov}\left(Z_i, Z_j\right) = \frac{n_{E\bullet} n_{C\bullet}}{n^3}\left(nS_{\bullet,ij} - S_{\bullet i} S_{\bullet j}\right)$$

where $S_{\bullet i}$ is the number of patients succeeding on the i^{th} scale, $S_{\bullet j}$ the number succeeding on the j^{th} scale and $S_{\bullet,ij}$ the number succeeding on *both* scales (Pocock, Geller and Tsiatis, 1987)

The ordinal case, no covariates

	E	C	Total
Best (A_1)	n_{E1}	n_{C1}	$n_{\bullet 1}$
$\vdots$	$\vdots$	$\vdots$	$\vdots$
Worst (A_a)	n_{Ea}	n_{Ca}	$n_{\bullet a}$
Total	$n_{E\bullet}$	$n_{C\bullet}$	n

$$Z = \frac{1}{n}\sum_{u=1}^{a} n_{Eu}\left(W_{Cu} - B_{Cu}\right) \quad \text{and} \quad V = \frac{n_{E\bullet}n_{C\bullet}}{3n}\left\{1 - \sum_{u=1}^{a}\left(\frac{n_{\bullet u}}{n}\right)^3\right\}$$

where $B_{Cu} = n_{C1} + \ldots + n_{C(u-1)}$ and $W_{Cu} = n_{C(u+1)} + \ldots + n_{Ca}$

Covariance between Z_i and Z_j

For two such statistics, we have

$$C_{ij} = \frac{n_{E\bullet} n_{C\bullet}}{n^2} \sum_{f,g,v,w} \delta_{fv} \delta_{gw} \left(H_{fg} H_{vw} + n_{E\bullet} K_{fg} H_{vw} + n_{C\bullet} H_{fg} K_{vw} \right)$$

where $\delta_{fv} = -1$, 0 or 1 if f <, =, > v respectively,

$K_{fg} = n_{\bullet f,i}\, n_{\bullet g,j}/n^2$, $H_{fg} = n_{\bullet fg,ij}/n - K_{fg}$,

$n_{\bullet fg,ij}$ is the count of patients who are both in category $A_{f,i}$ on scale Σ_i and in category $A_{g,j}$ on scale Σ_j

Adjustment for covariates

For ordinal data, the score statistic Z_i is now

$$Z_i = \sum_{q=1}^{n}\sum_{u=1}^{a}\gamma_q\left(y_{ui,q} - \hat{p}_{ui,q}\right)\left(W_{ui,q} - B_{ui,q}\right)$$

and, approximately,

$$C_{ij} \approx \frac{n_{\bullet E}n_{\bullet C}}{n^2}\sum_{q=1}^{n}\sum_{u=1}^{a}\sum_{v=1}^{a}\left(W_{ui,q} - B_{ui,q}\right)\left(W_{vj,q} - B_{vj,q}\right)\hat{p}_{ui,vj,q}$$

For the q^{th} patient $\gamma_q = 1$ if on E and $y_{ui,q} = 1$ if A_u on i^{th} scale

$\hat{p}_{ui,q}$ is fitted probability that $y_{ui,q} = 1$, $B_{ui,q} = \hat{p}_{1i,q} + \ldots + \hat{p}_{(u-1)i,q}$

and $W_{ui,q} = \hat{p}_{(u+1)i,q} + \ldots + \hat{p}_{ai,q}$

$\hat{p}_{ui,vj,q}$ is fitted probability that $y_{ui,q} = 1$ *and* $y_{vj,q} = 1$

Fitted probabilities

The $\hat{p}_{ui,q}$ are fitted probabilities from marginal proportional odds regression models

Each $\hat{p}_{ui,vj,q}$ is a fitted probability from a binary logistic regression model of the indicator that the q^{th} patient is in A_u on the i^{th} scale *and* in A_v on the j^{th} scale

– *this involves many logistic regression models!*

This corresponds the the empirical estimation of covariances used in the GEE approach

Analyses of a synthetic stroke dataset, n = 1000

	Adjusting	Method	Z*	V*	$\hat{\theta}$	$sd(\hat{\theta})$	p
	no factors	GEE	15.55	68.19	0.2280	0.1211	0.0597
		score	15.57	68.94	0.2259	0.1204	0.0607
	all factors	GEE	17.27	60.09	0.2874	0.1290	0.0259
binary		score	17.84	62.85	0.2839	0.1261	0.0244
	all factors +	GEE	Failed to converge				
	centre	score	19.64	58.23	0.3373	0.1311	0.0100
	no factors	GEE	9.02	89.85	0.1004	0.1055	0.3413
		score	7.84	83.92	0.0935	0.1092	0.3918
	all factors	GEE	17.15	89.17	0.1923	0.1059	0.0695
ordinal		score	15.18	82.41	0.1842	0.1102	0.0945
	all factors +	GEE	20.96	79.86	0.2624	0.1119	0.0190
	centre	score	18.49	80.33	0.2302	0.1116	0.0391

Results from 10,000-fold simulations of the combined score test and the GEE approach

sample size	hypothesis	true θ	# rejections according to			$\hat{\theta}$ from	
			score	GEE	both	score	GEE
200	H_0	0	232	268	228	0.002	0.002
	H_1	0.781	9170	9186	9122	0.795	0.808
500	H_0	0	251	255	239	–0.001	–0.001
	H_1	0.494	8950	8942	8894	0.480	0.472
1000	H_0	0	227	226	211	0.000	0.000
	H_1	0.349	9010	8995	8956	0.345	0.334

Extensions

Expressions for $\mathrm{cov}(Z_i, Z_j)$ can also be found when Z_i and Z_j are score statistics for normally distributed data or Poisson data, including cases when each relates to a different data type

We have done this for the case without covariates, but not yet with covariate adjustments

The case of survival data is harder – Zakiyah Zain is trying for interval-censored survival data (she will talk on this tomorrow!)

References

Pocock, S.J., Geller, N. L. and Tsiatis, A. A. (1987). The analysis of multiple endpoints in clinical trials. *Biometrics* **43**, 487-498.

Tilley, P. C., Marler, J., Geller, N. L., Lu, M., Legler, J., Brott, T., Lyden, P. and Grotta, J. for the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Trial Study Group. (1996). Use of a global test for multiple outcomes in stroke trials with application to the National Institute of Neurological Disorders and t-PA Stroke Trial. *Stroke* **27,** 2136-2142.