

Competing risks in anti-epileptic drug trials

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Acknowledgments

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Outline

- AED trial/Data
- Competing risks in AED trials
- Logrank vs Gray's test
- Titration adjustment in AED trials

Epilepsy

- Characterised by seizures
- Common neurological condition with prevalence of around 0.5-1%
- Newly diagnosed usually prescribed single anti-epileptic drug (AED) treatment
- AED considered successful if the person taking it becomes seizure free with few side effects

Data

- SANAD (Standard and new antiepileptic drugs) trial – recruited \approx 2500
- Carbamazepine (CBZ) – standard AED
- New AEDs - Lamotrigine (LTG), Gabapentin, Oxcarbazepin, Topiramate
- LTG vs. CBZ (n = 605)

Time to treatment failure in AED trials

- Defined as the time to withdraw randomised AED or addition of another
- Recommended as a primary outcome in RCTs by ILAE

Competing risks

- Reasons for withdrawal/treatment failure
 - (1) Inadequate seizure control (ISC)
 - (2) Unacceptable adverse effects (UAE)
- Newer AEDs: non-inferior seizure control, improved side effect profiles
- Tolerance of side effects varies across populations

Question of interest

- Is LTG superior to CBZ in terms of UAE? ISC?
 - Is LTG more tolerable?
 - Is LTG better in seizure control?

Standard methods

- Overall treatment failure analysis – common in the AED field
- Fail to examine differential effects of AEDs on the reason of withdrawal
- Assumes reasons of failure are of equal importance (which may not be the case)
- Different consequences e.g. loss of driving license vs common side effects such as rash

Analysing competing risks

Logrank vs. Gray's test

- Logrank test compares cause-specific hazards
- Gray's test compares cumulative incidence curves

Logrank vs. Gray's test

Previous work:-

- Friedlin and Korn (2005): simulation study – concluded logrank test is preferable
- Gichangi and Vach (2006) – use both approaches
- And others.
 - (i) focused on one main event type of interest
 - (ii) competing events **positively** correlated

Logrank or Gray's test?

- In epilepsy/AED field
 - Both event types are of interest
 - Events may be **negatively** correlated
 - Degree of correlation differ between AEDs

Simulation results: small adverse effect on ISC, moderate beneficial effect on UAE**

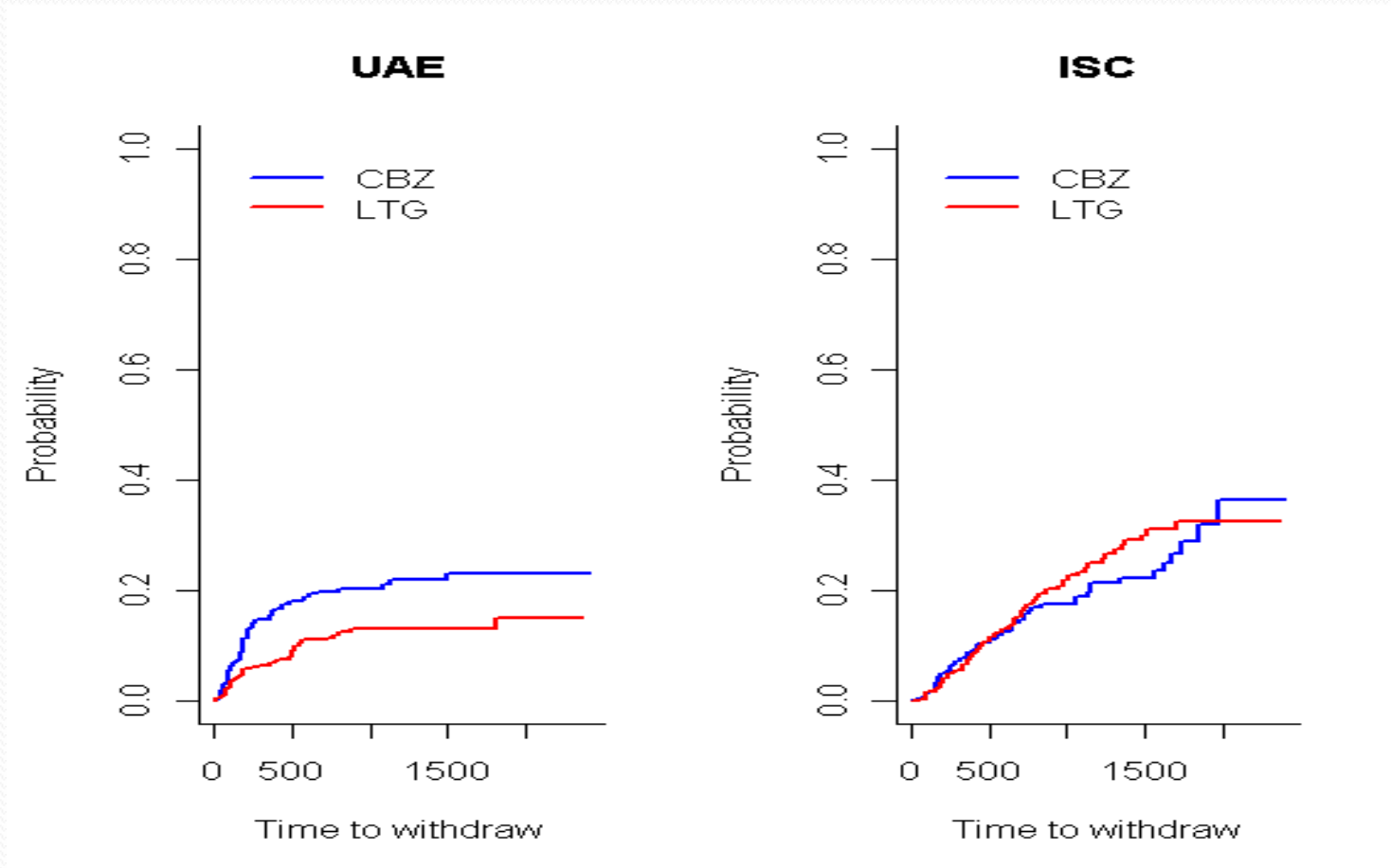
Correlation between events		W^{h_1}	W^{h_2}	W^{I_1}	W^{I_2}	W^0	Log rank test for both event types	Gray's test for both event types
A	B							
0	-0.8	0.7887	1.0000	0.2276	0.9932	1.0000	0.7887	0.2274
	-0.2	0.0653	0.9989	0.8598	0.9850	0.9442	0.0651	0.8597
	0	0.2916	0.9916	0.9414	0.9877	0.6646	0.2892	0.9412
-0.2	-0.8	0.5687	1.0000	0.3456	0.9872	0.9999	0.5687	0.3454
	-0.2	0.2027	0.9831	0.8958	0.9759	0.6705	0.1995	0.8953
	0	0.5751	0.9336	0.9593	0.9812	0.2396	0.5350	0.9576
-0.5	-0.5	0.1052	0.9791	0.8163	0.9490	0.7182	0.1025	0.8161
	-0.2	0.6435	0.7870	0.9319	0.9553	0.0867	0.5066	0.9252
	0	0.9194	0.5378	0.9740	0.9596	0.0923	0.4950	0.9543
-0.8	-0.8	0.0505	0.9825	0.7138	0.9285	0.8357	0.0499	0.7136
	-0.2	0.9702	0.1942	0.9613	0.8825	0.3727	0.1906	0.8804
	0	0.9978	0.0696	0.9886	0.8700	0.7852	0.0695	0.8700

- Gray's test has greater power than logrank test to detect treatment differences in negatively correlated settings

**Williamson PR, Kolamnunnage-Dona R and Tudur Smith C.

The influence of competing risks setting on the choice of hypothesis test for treatment effect. Biostatistics 2006.

Cumulative incidence curves



UAE test statistic = 10.38,
1df, $p = 0.0012$

ISC test statistic = 0.787,
1df, $p = 0.375$

Question of interest

- Is LTG superior to CBZ in terms of UAE? ISC?
 - LTG significantly more tolerable than CBZ
 - LTG similar in terms of seizure control
- Concluded by SANAD study group in 2007.

Biased in favour of newer drug?

- Not blinded
- CBZ considered to have been titrated more quickly - brings benefits in terms of seizure control, but more likely to cause adverse effects

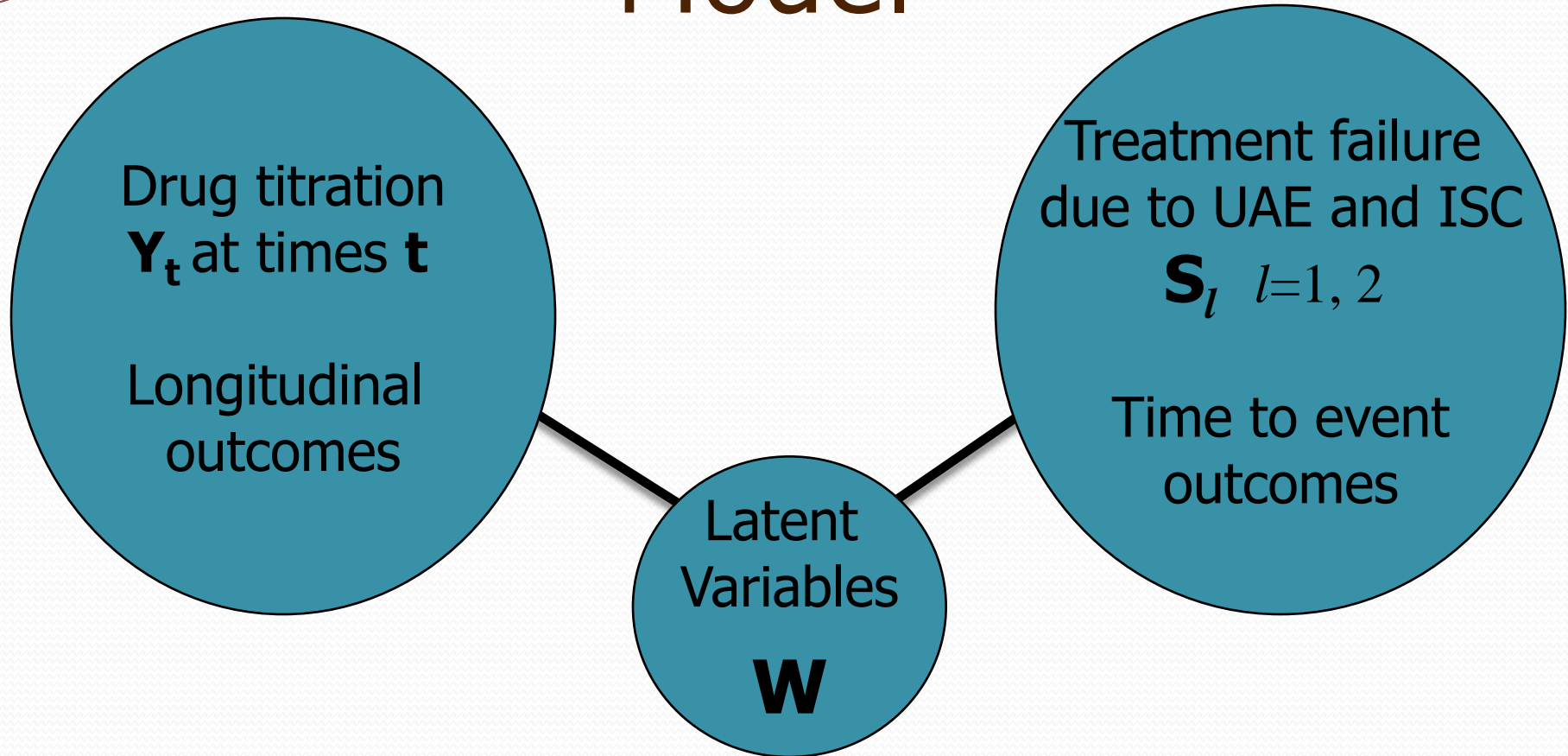
Effect of drug titration

- Investigate the effect of drug titration on the relative effects of LTG and CBZ on treatment failure
- Is LTG superior to CBZ after adjusting for titration in terms of UAE? ISC?

Drug Titration

- Calibrated dose - Standardise the dose of each drug relative to the midpoint of the maintenance dose range for that particular drug
- The maintenance dose range recommended in SANAD was independently deemed to be reasonable and the approach to calibration considered sensible

Model



- Association between longitudinal and survival data via latent processes

Competing risks joint model

- Longitudinal process

$$Y_t = X_{1i}(t)\beta_1 + W_{1i}(t) + \varepsilon_t$$

- Survival process – cause-specific hazards sub-model for the l^{th} cause of failure

$$\lambda^{(l)}(t | X_2, W_2) = \lambda_0^{(l)}(t) \exp\{X_{2i}(t)\beta_2^{(l)} + W_{2i}^{(l)}(t)\}, l = 1, 2$$

- Two processes are assumed to be conditionally independent given W_1 and W_2

Competing risks joint model

- Assume proportional association

$$W_{2i}^{(l)}(t) = \gamma^{(l)} W_{1i}(t)$$

- $\gamma^{(l)}$ indicate the level of association between the survival and longitudinal components
- Eg. $W_1(t) = U_0 + U_1 t$

Likelihood function

$$L(Y, \theta, \eta) = L_Y(Y, \theta) \prod_{l=1}^K L^{(l)}_{\eta|Y}$$

where

$$L^{(l)}_{\eta|Y} = E_{W_2^{(l)}|Y} \{ L_{\eta|W_2^{(l)}}(\theta, \eta = l | W_2^{(l)}) \}$$

$$\eta \in (1, \dots, K)$$

K=2 here

EM algorithm

- Random effects are treated as missing data
- Plausible starting values – estimates from separate analyses of the longitudinal and competing risk components

E-step

- Expectation of the complete data log-likelihood is evaluated, conditioning on both the observed data and the current parameter estimates

E-step

- $W_{2i}^{(l)}(t) = \gamma^{(l)} W_{1i}(t)$
- Partial likelihood (PL) is formulated as

$$PL = \prod_{i=1}^n \left\{ \frac{\exp(X_i' \beta^{(l)}) Z_i^{(l)}(t)}{\sum_{j \in R_i} \exp(X_j' \beta^{(l)}) Z_j^{(l)}(t)} \right\}^{\delta_i^{(l)}}$$

where $\exp(W_2^{(l)}(t)) = Z^{(l)}(t)$

$\delta = l$ if $\eta = l$, 0 otherwise

M-step

- Parameter estimates are obtained via maximisation of the expected log-likelihood
- Hazard for each risk is updated using

$$\hat{\lambda}_0^{(l)}(\nu) = \sum_{i=1}^n \left\{ \frac{\delta_i^{(l)} I(T_i = \nu)}{\sum_{j=1}^n E_j[\exp\{X_j' \beta^{(l)} + \gamma^{(l)} W_{1j}(\nu)\}] V_j(\nu)} \right\}$$

where $V_j(\nu)$ is an indicator equivalent to $I(T_i > \nu)$

M-Step: evaluate expectation

- Require the density $f(W|Y, S_1, S_2)$
- Exploit the conditional independence between the longitudinal process and each event type

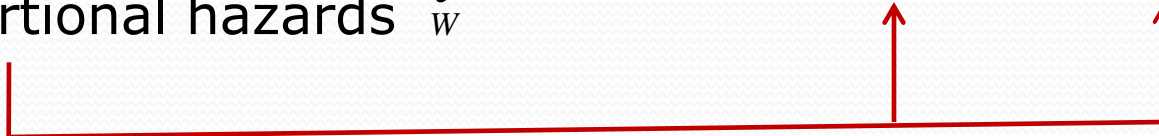
$$f(W | S_1, S_2, Y, \hat{\theta}) = \frac{f(W | Y, \hat{\theta}) f(S_1, S_2 | W, Y, \hat{\theta})}{f(S_1, S_2 | Y, \hat{\theta})}$$

$$= \frac{f(W | Y, \hat{\theta}) f(S_1 | W, Y, \hat{\theta}) f(S_2 | S_1, W, Y, \hat{\theta})}{f(S_1 | Y, \hat{\theta}) f(S_2 | S_1, Y, \hat{\theta})}$$

Gaussian

$$= \frac{f(W | Y, \hat{\theta}) f(S_1 | W, \hat{\theta}) f(S_2 | W, \hat{\theta})}{\int_w f(W | Y, \hat{\theta}) f(S_1 | W, \hat{\theta}) f(S_2 | W, \hat{\theta})}$$

Follow
proportional hazards



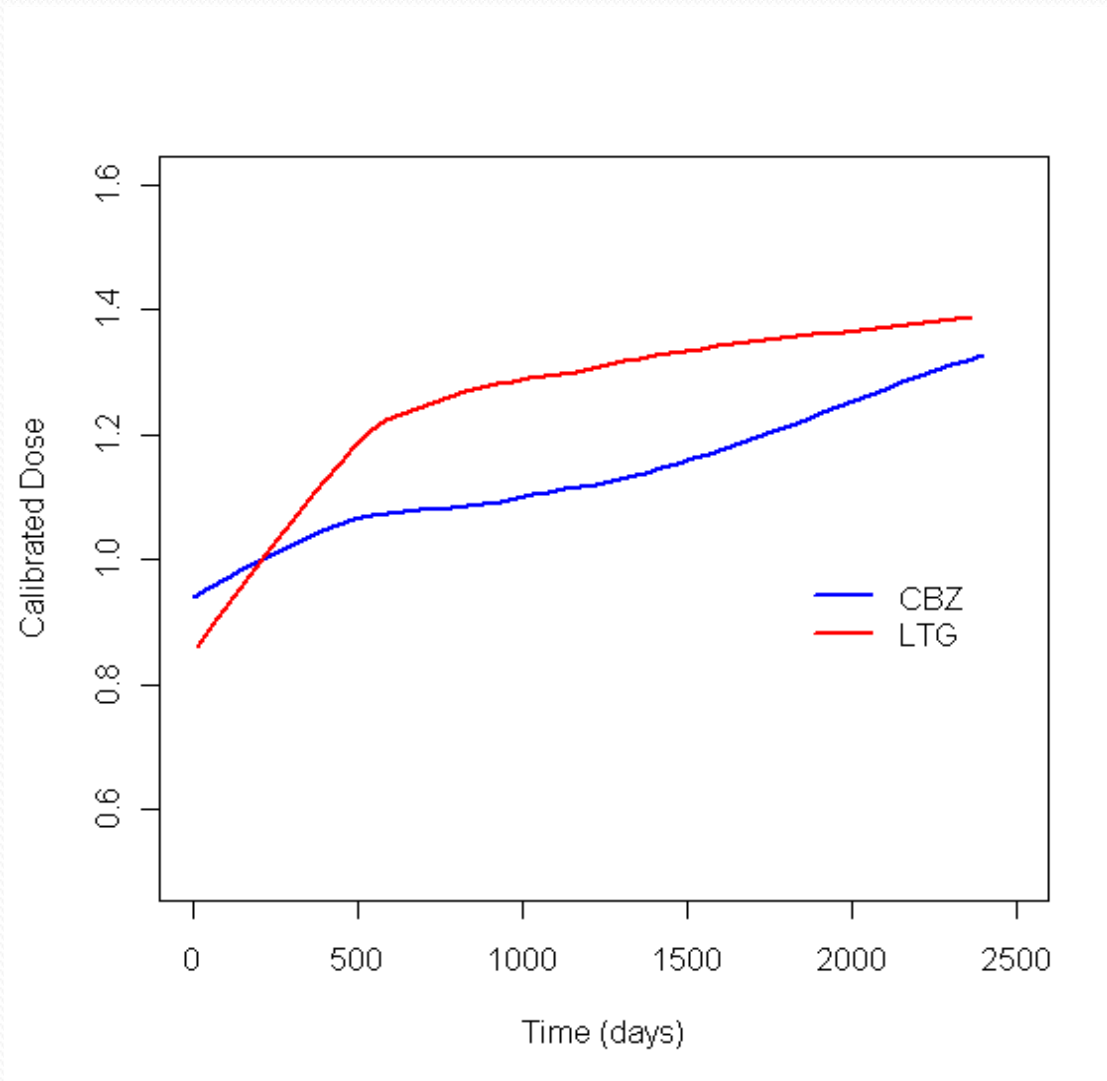
Software

- Developed in R
- Proposed EM algorithm converged in < 4 min
- Available in R's **joineR** library soon!

Application

After adjusting for titration, is LTG still superior to CBZ in terms of UAE/ISC??

Mean profiles of calibrated dose for CBZ and LTG



Longitudinal Model

Piecewise (2-slope) model

- Change-point at 500 days

- New time scale

$$d_t = t - 500$$

- Let

$$\zeta_t = \begin{cases} 1 & \text{if } t \leq 500 \\ 0 & \text{if } t > 500 \end{cases}$$

Piecewise (2 slope) model

$$Y_t = \beta_0 + \zeta_t d_t \beta_{11} + (1 - \zeta_t) d_t \beta_{12} \\ + X_{1i} \zeta_t \beta_{21} + X_{1i} (1 - \zeta_t) \beta_{22} + W_{1i}(t) + \varepsilon_t$$

where

$$W_{1i}(t) = U_{0i} + \zeta_t d_t U_{1i} + (1 - \zeta_t) d_t U_{2i}$$

$$\begin{pmatrix} U_{0i} \\ U_{1i} \\ U_{2i} \end{pmatrix} \sim N_3 \left\{ \begin{pmatrix} 0 \\ 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \nu_{00} & \nu_{01} & \nu_{02} \\ \nu_{10} & \nu_{11} & \nu_{12} \\ \nu_{20} & \nu_{21} & \nu_{22} \end{pmatrix} \right\}$$

Competing risks joint model estimates (longitudinal component)

Parameter	coef (95% CI)	coef (95% CI)
Intercept	2.2870 (2.129, 2.452)	
	Before 500 days	After 500 days
Time (Slope)	0.0009 (0.0006, 0.0012)	0.0000 (-0.0003, 0.0001)
Drug LTG vs CBZ	0.2580 (-0.002, 0.477)	0.3000 (0.023, 0.540)
Drug x Time interaction	0.0009 (0.0005, 0.0014)	0.0002 (-0.0001, 0.0005)

Competing risks joint model estimates (survival component)

Parameters	Competing risks joint analysis	Separate analysis*
UAE: LTG vs CBZ HR (95% CI)	0.519 (0.358, 0.789)	0.545 (0.359, 0.826)
$\gamma^{(1)}$ (95% CI)	-0.579 (-0.890, -0.289)	
ISC: LTG vs CBZ HR (95% CI)	1.004 (0.709, 1.397)	1.020 (0.709, 1.450)
$\gamma^{(2)}$ (95% CI)	0.282 (0.167, 0.396)	

* Fitting cause-specific model to each competing event alone (as in Marson, 2007)

Question of interest

- Is LTG superior to CBZ after adjusting for titration in terms of UAE? ISC?
 - LTG significantly more tolerable than CBZ
 - LTG similar in terms of seizure control
- LTG still superior to CBZ
- Original conclusion robust

References

- Williamson PR, Kolamnunnage-Dona R, Philipson P, Marson AG. Joint modelling of longitudinal and competing risks data. *Statistics in Medicine* (accepted)
- Williamson PR, Kolamnunnage-Dona R, Tudur Smith C. The influence of competing risks setting on the choice of hypothesis test for treatment effect. *Biostatistics* 2006; doi: 10.1093/biostatistics/kxl040.
- Williamson PR, Tudur Smith C, Sander JW, Marson AG. Importance of competing risks in the analysis of anti-epileptic drug failure. *Trials* 2007, 8:12 doi: 10.1186/1745-6215-8-12.
- Marson AG et al, on behalf of the SANAD Study group (2007). Carbamazepine, gabapentin, lamotrigine, oxcarbazepine or topiramate for partial epilepsy: results from the SANAD trial. *Lancet* 369: 1000-1015, doi: 10.1016/S0140-6736(07)60460-7.