Statistical Models for Censored Point Processes with Cure Rates

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Outline

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Epilepsy

- Defined as the occurrence of recurrent, unprovoked seizures.
- ILAE classification scheme divides seizures into partial, generalised or unclassified seizures.
- Partial - part of the brain; simple or complex; motor, sensory, occipital, frontal lobe and temporal lobe. Can sometimes occur with secondary generalisation
- Generalised - all of the brain; tonic-clonic (grand mal), absence (petit mal), myoclonic and atonic

Early Epilepsy and Single Seizures

- On average 50% of people do not experience a recurrence following a first seizure
- Around $20 - 30\%$ of people will never achieve long-term remission

- Antiepileptic drugs (AEDs) come with unpleasant side effects
- In early epilepsy are AEDs necessary?

The MESS Trial

- MRC Multicentre Trial for Early Epilepsy and Single Seizures
- Comparison of policies: immediate vs deferred treatment
- Randomised 1443 patients
- Eligibility criteria:

- Outcomes of interest - time to first seizure, time to second seizure

(Marson et al. 2005)

The MESS Trial

- MRC Multicentre Trial for Early Epilepsy and Single Seizures
- Comparison of policies: immediate vs deferred treatment
- Randomised 1443 patients
- Eligibility criteria:
  1. Aged at least one month
- Outcomes of interest - time to first seizure, time to second seizure

(Marson et al. 2005)

The MESS Trial

- MRC Multicentre Trial for Early Epilepsy and Single Seizures
- Comparison of policies: immediate vs deferred treatment
- Randomised 1443 patients
- Eligibility criteria:
  2. Had experienced at least one epileptic seizure
- Outcomes of interest - time to first seizure, time to second seizure

(Marson et al. 2005)

The MESS Trial

- MRC Multicentre Trial for Early Epilepsy and Single Seizures
- Comparison of policies: immediate vs deferred treatment
- Randomised 1443 patients
- Eligibility criteria:

  3. Uncertainty about whether to proceed with treatment
- Outcomes of interest - time to first seizure, time to second seizure

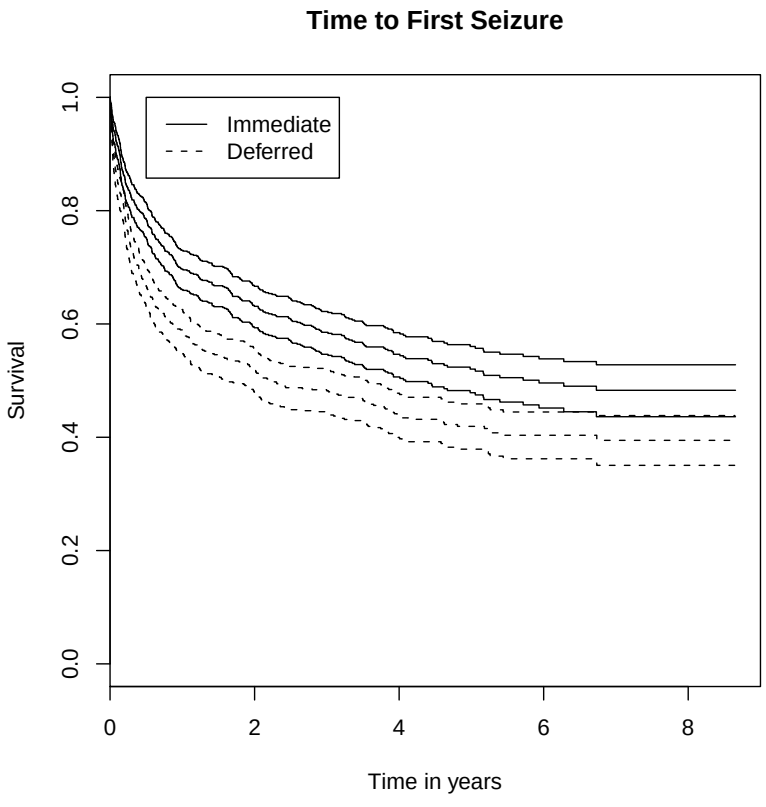
(Marson et al. 2005)

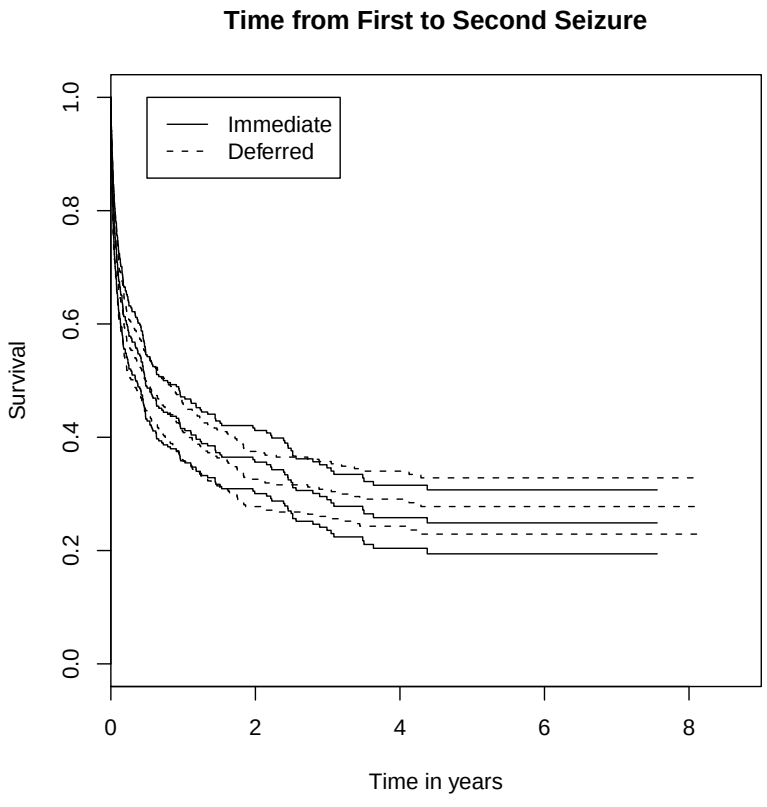
Outline

Seizure Type Pre-Randomisation

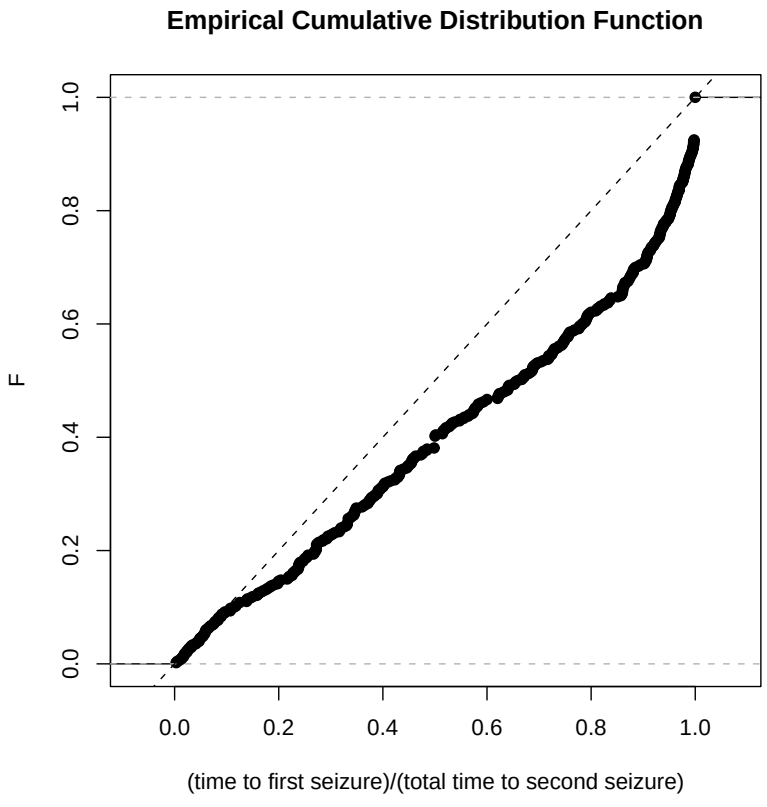
Seizure Type	Immediate	Deferred
Tonic-Clonic	375	406
Partial with 2° Tonic-Clonic	239	215
Partial	51	52
Generalised	21	19
Other	17	13

Kaplan-Meier Curves by Treatment

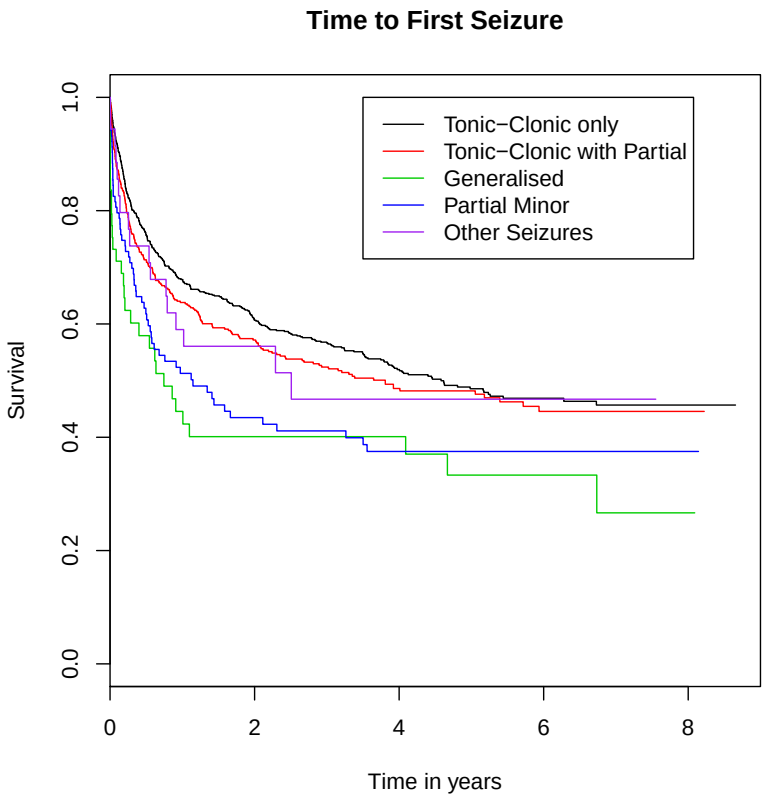


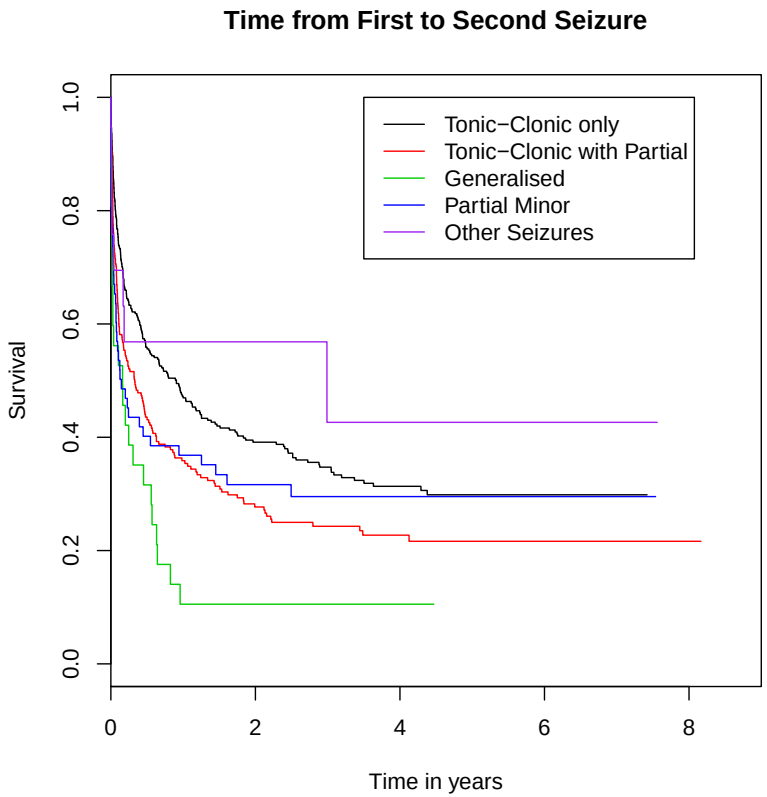


Cumulative Distribution Function



Kaplan-Meier Curves by Seizure Type





Accelerated Failure Time Assumption

P-H assumption, for individual i

$$h_i(t) = e^{\beta' z_i} h_0(t) \tag{1}$$

Epilepsy data well modelled by distributions that are AFT

$$S_i(t) = S_0(t/e^{\beta' z_i}) \tag{2}$$

(1) $e^{\beta' z_i}$ reflects impact of treatment on baseline hazard
(2) $e^{\beta' z_i}$ reflects impact of treatment on baseline time scale

Testing the AFT Assumption

$z = 0/1$ - allocated to deferred/immediate treatment

We define $t_0^{(a)}$, $t_1^{(a)}$, for $0 < a < 1$, by:

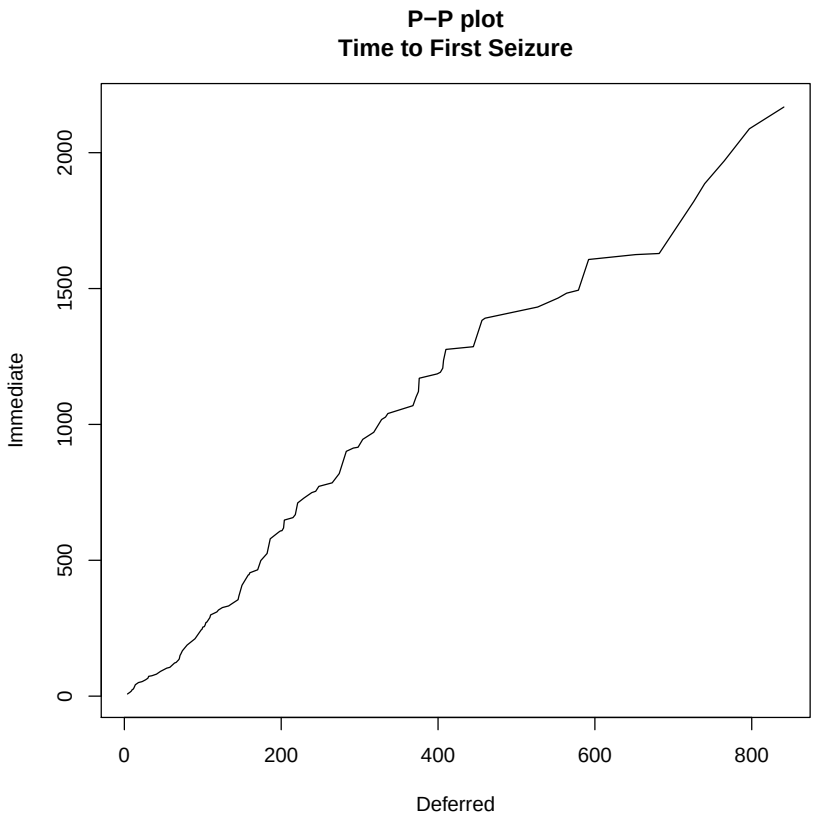
$$a = S_0(t_0^{(a)}) \qquad a = S_1(t_1^{(a)})$$

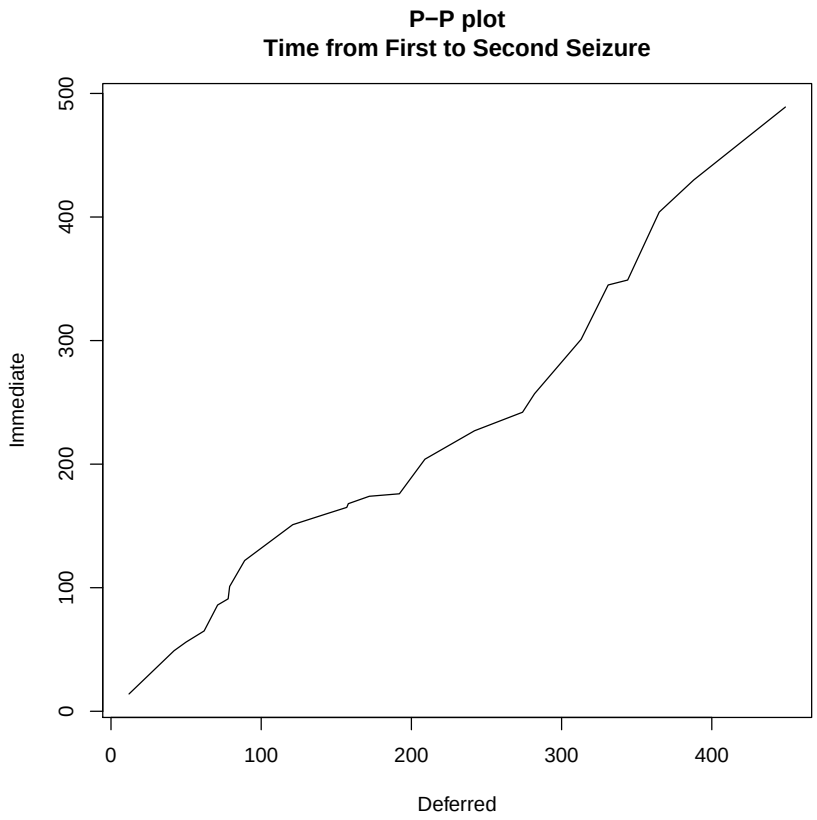
$$S_1(t_1^{(a)}) = S_0(t_0^{(a)})$$

Then by (2), $t_1^{(a)} = t_0^{(a)} e^{\beta}$

Percentile-percentile plot to test AFT assumption

Percentile-percentile plots





Weibull, Exponential, Log-logistic, Lognormal, Gamma,. . . .

Outline

The Data

Data arrives in two parts:

1. Pre-randomisation event count, X_i - the number of seizures in a given period of time prior to entry to the trial

2. Post-randomisation survival times, (Y_{1i}, Y_{2i}) - times to first and second seizure following randomisation to a treatment policy

Standard Approaches

- Treatment effects in recurrent events
  - Cook and Lawless (2007)
  - rates and mean functions, mixed Poisson model
- Use of baseline count data
  - Cook and Lawless (2007)
  - mixed Poisson processes
- If datasets exhibit cure rates, focus needs to be on gap times
- 'If I have a seizure, am I likely to have another one, and if so, when?'

Joint Model

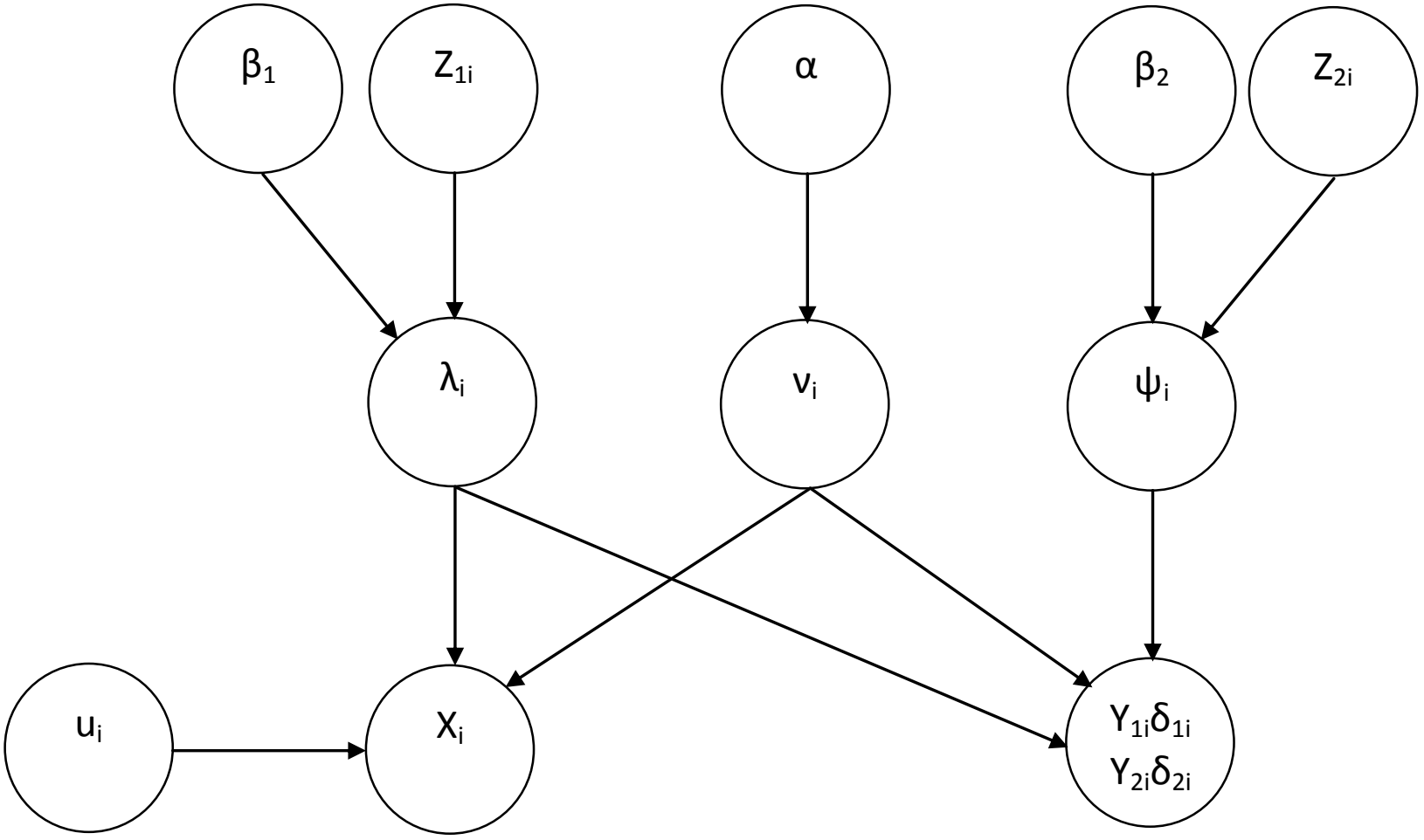
The joint model is specified by the following equations:

$$
\begin{aligned}
f_{X|\nu}(x_i \mid \nu_i; \lambda_i, u_i) &= \frac{(\lambda_i u_i \nu_i)^{x_i} \exp(-\lambda_i u_i \nu_i)}{x_i!} \\
f_{Y_j|\nu}(y_{ji} \mid \nu_i; \lambda_i, \psi_i) &= \lambda_i \psi_i \nu_i \exp(-\lambda_i \psi_i \nu_i y_{ji}),\ j = 1, 2 \\
g_\nu(\nu_i; \alpha) &= \frac{\alpha^\alpha \nu_i^{\alpha-1} \exp(-\alpha \nu_i)}{\Gamma(\alpha)}
\end{aligned}
$$

$\lambda_i = \exp(\beta_1' \boldsymbol{z}_{1i})$, $\psi_i = \exp(\beta_2' \boldsymbol{z}_{2i})$, α determines degree of heterogeneity

(Cowling et al. 2006)

Graphical Representation



Unconditional Distributions

- Unconditional distribution of X_i is Negative Binomial
- Unconditional joint survivor function of the Y_{ji}, $j = 1, 2$ is bivariate Lomax

$$f_{Y_1,Y_2}(y_{1i}, y_{2i}; \lambda_i, \psi_i, \alpha) = \frac{\alpha+1}{\alpha}(\lambda_i\psi_i)^2\left\{1 + \frac{\lambda_i\psi_i(y_{1i}+y_{2i})}{\alpha}\right\}^{-(\alpha+2)}$$

$$S_{Y_1,Y_2}(y_{1i}, y_{2i}; \lambda_i, \psi_i, \alpha) = \left\{1 + \frac{\lambda_i\psi_i(y_{1i}+y_{2i})}{\alpha}\right\}^{\alpha}$$

- Unconditional marginals are univariate Lomax

Log-Logistic and Lomax distributions

- Log-logistic (shape=a, scale=b)

$$F_Y(y_i) = 1 - \{1 + (y_i/b)^a\}^{-1} \tag{3}$$

- Lomax (shape=a, scale=b)

$$F_Y(y_i) = 1 - \{1 + (y_i/b)\}^{-a} \tag{4}$$

When $a = 1$, (3) and (4) are equivalent

Log-Logistic Distribution

Survivor function

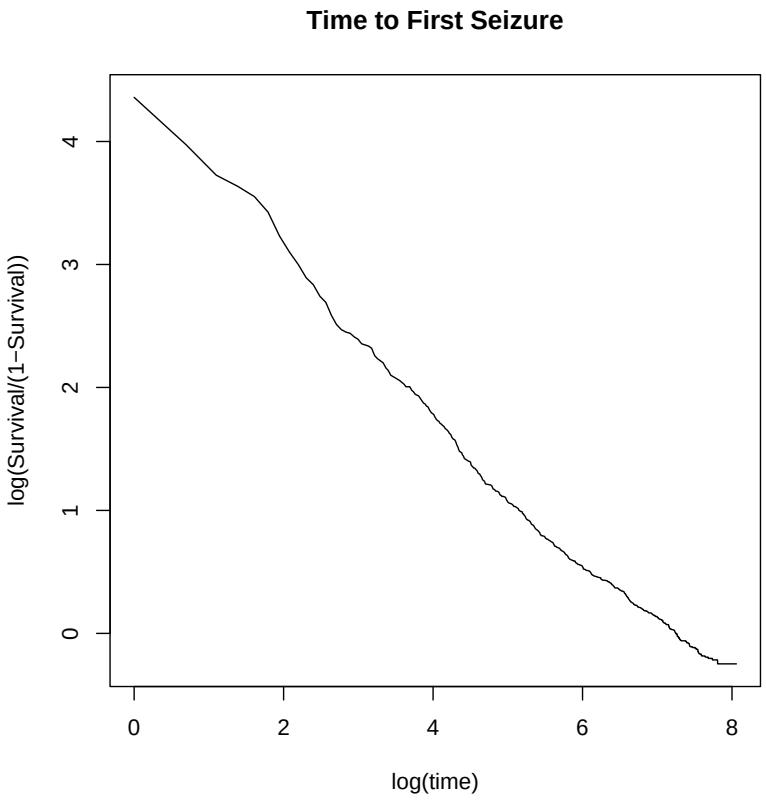
$$S(y) = \frac{1}{1 + (y/b)^a}$$

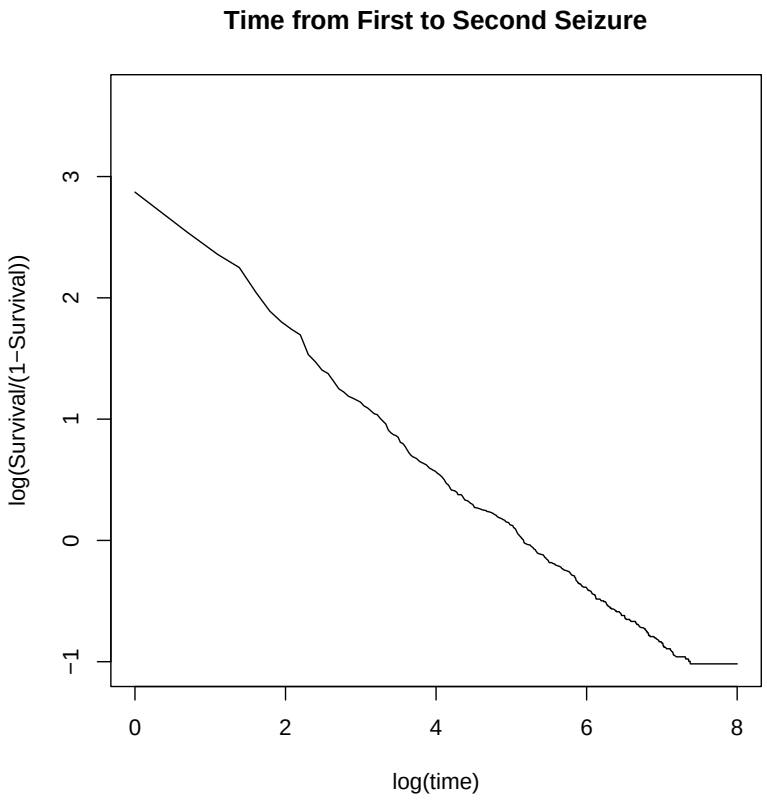
Consider the following transformation:

$$\ln\left\{\frac{S(y)}{1 - S(y)}\right\} = -a\ln(y) + a\ln(b)$$

Linear in $\ln(y)$

Justifying the Log-Logistic Distribution





Log-Likelihood

Three different scenarios:

1. Y_{1i} and Y_{2i} both observed,
2. Y_{1i} is observed, but Y_{2i} is censored, and
3. Y_{1i} is censored

Straightforward to derive log-likelihood and derivatives allowing inference using a numerical method such as Newton-Raphson

Pre-Randomisation Seizure Rates

Seizure Type	$\widehat{\lambda}_i$ (95% C.I.)	Expected yearly rate
Tonic-Clonic	0.005 (0.005,0.006)	2
2° Tonic-Clonic	0.008 (0.007,0.009)	3
Partial	0.016 (0.013,0.019)	6

Change in Seizure Rates, Post-Randomisation

Seizure Type	$\widehat{\psi}_i$ (95% C.I.)			
	Abnormal EEG			
	Immediate		Deferred	
Tonic-Clonic	0.122	(0.10,0.15)	0.188	(0.15,0.23)
2° Tonic-Clonic	0.127	(0.10,0.16)	0.282	(0.22,0.36)
Partial	0.078	(0.05,0.12)	0.074	(0.05,0.11)
	Normal EEG			
	Immediate		Deferred	
Tonic-Clonic	0.127	(0.10,0.15)	0.134	(0.11,0.16)
2° Tonic-Clonic	0.089	(0.07,0.11)	0.135	(0.11,0.17)
Partial	0.195	(0.12,0.32)	0.127	(0.08,0.21)

Outline

Recall...

- Risk of future seizures increases with the number of previous seizures
  - Clustering and different treatment effects
  - Time-varying seizure rate
- On average 50% of people do not experience a recurrence after a single seizure
  - Large reductions in seizure rates
  - Cure rate models

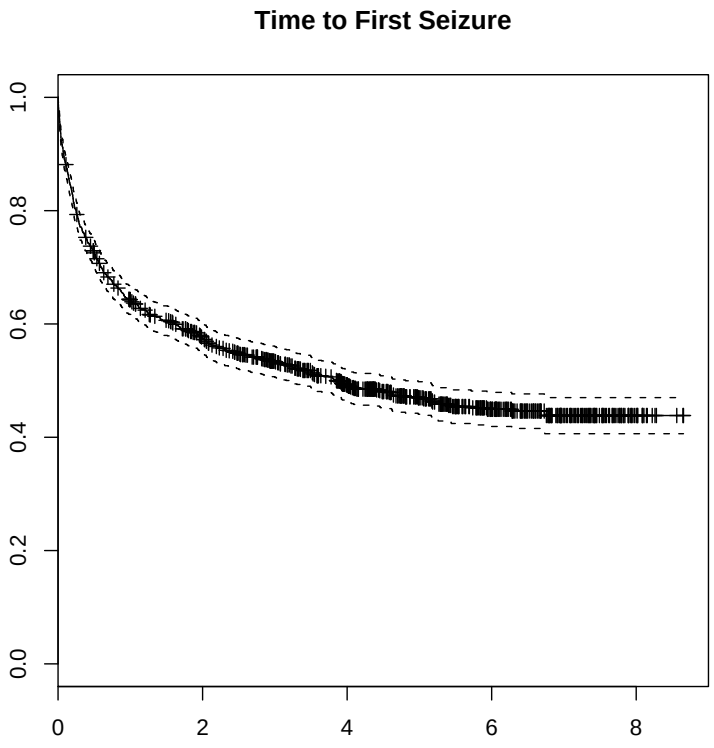
Removal of the Post-Randomisation IID Assumption

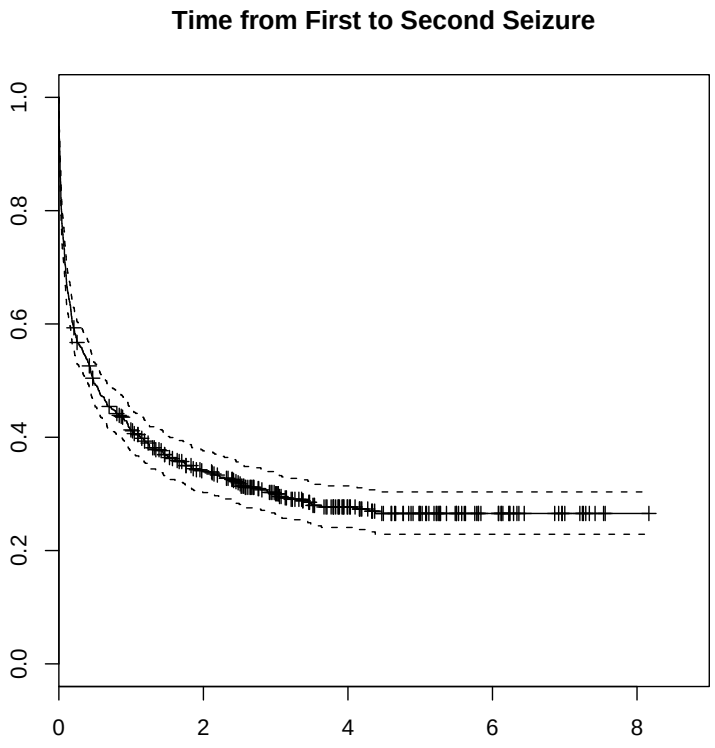
Evidence to suggest that ψ_i may change through time

$$
\begin{aligned}
f_{X|\nu}(x_i \mid \nu_i; \lambda_i, u_i) &= \frac{(\lambda_i u_i \nu_i)^{x_i} \exp(-\lambda_i u_i \nu_i)}{x_i!} \\
f_{Y_1|\nu}(y_{1i} \mid \nu_i; \lambda_i, \psi_{1i}) &= \lambda_i \psi_{1i} \nu_i \exp(-\lambda_i \psi_{1i} \nu_i y_{1i}) \\
f_{Y_2|\nu}(y_{2i} \mid \nu_i; \lambda_i, \psi_{1i}, \psi_{2i}) &= \lambda_i \psi_{1i} \psi_{2i} \nu_i \exp(-\lambda_i \psi_{1i} \psi_{2i} \nu_i y_{2i}) \\
g_\nu(\nu_i; \alpha) &= \frac{\alpha^\alpha \nu_i^{\alpha-1} \exp(-\alpha \nu_i)}{\Gamma(\alpha)}
\end{aligned}
$$

$\lambda_i = \exp(\beta_1' \boldsymbol{z}_{1i})$, $\psi_{1i} = \exp(\beta_2' \boldsymbol{z}_{2i})$ and $\psi_{2i} = \exp(\beta_3' \boldsymbol{z}_{3i})$

Kaplan-Meier Curves





Inclusion of a Cure Fraction

Large proportion of individuals 'immune' from future seizures

$$
\begin{aligned}
f_{X|\nu}(x_i \mid \nu_i; \lambda_i, u_i) &= \frac{(\lambda_i u_i \nu_i)^{x_i} \exp(-\lambda_i u_i \nu_i)}{x_i!} \\
f_{Y_j|\nu}(y_{ji} \mid \nu_i; \lambda_i, \psi_i, p_{ji}) &= p_{ji} \lambda_i \psi_i \nu_i \exp(-\lambda_i \psi_i \nu_i y_{ji}) \\
S_{Y_j|\nu}(y_{ji} \mid \nu_i; \lambda_i, \psi_i, p_{ji}) &= 1 - p_{ji} + p_{ji} \exp(-\lambda_i \psi_i \nu_i y_{ji}) \\
g_\nu(\nu_i; \alpha) &= \frac{\alpha^\alpha \nu_i^{\alpha-1} \exp(-\alpha \nu_i)}{\Gamma(\alpha)}
\end{aligned}
$$

$\lambda_i = \exp(\beta_1' \boldsymbol{z}_{1i})$, $\psi_i = \exp(\beta_2' \boldsymbol{z}_{2i})$ and $p_{ji} = \frac{\exp(\kappa_j' \boldsymbol{w}_{ji})}{1+\exp(\kappa_j' \boldsymbol{w}_{ji})}$

Cure Rate

Seizure Type	$1 - \widehat{p}_{1i}$ (95% C.I.)			
	Abnormal EEG			
	Immediate		Deferred	
Tonic-Clonic	0.518	(0.45,0.59)	0.360	(0.20,0.43)
2° Tonic-Clonic	0.389	(0.31,0.48)	0.250	(0.19,0.33)
Partial	0.487	(0.36,0.62)	0.332	(0.22,0.46)
	Normal EEG			
	Immediate		Deferred	
Tonic-Clonic	0.528	(0.47,0.59)	0.511	(0.45,0.57)
2° Tonic-Clonic	0.584	(0.51,0.65)	0.568	(0.50,0.64)
Partial	0.345	(0.20,0.52)	0.330	(0.19,0.50)

$1 - \widehat{p}_{2i} = 0.26$ for all i

Change in Seizure Rates, Following Randomisation

Seizure Type	$\widehat{\psi}_{1i}$ (95% C.I.) first seizure			
	Abnormal EEG			
	Immediate		Deferred	
Tonic-Clonic	0.347	(0.26,0.47)	0.738	(0.57,0.95)
2° Tonic-Clonic	0.326	(0.24,0.44)	0.786	(0.58,1.06)
Partial	0.522	(0.31,0.88)	0.695	(0.41,1.18)
	Normal EEG			
	Immediate		Deferred	
Tonic-Clonic	0.582	(0.45,0.75)	0.683	(0.53,0.87)
2° Tonic-Clonic	0.467	(0.34,0.65)	0.622	(0.46,0.84)
Partial	0.522	(0.27,1.00)	0.384	(0.20,0.73)

Change in Seizure Rates, Following First Seizure

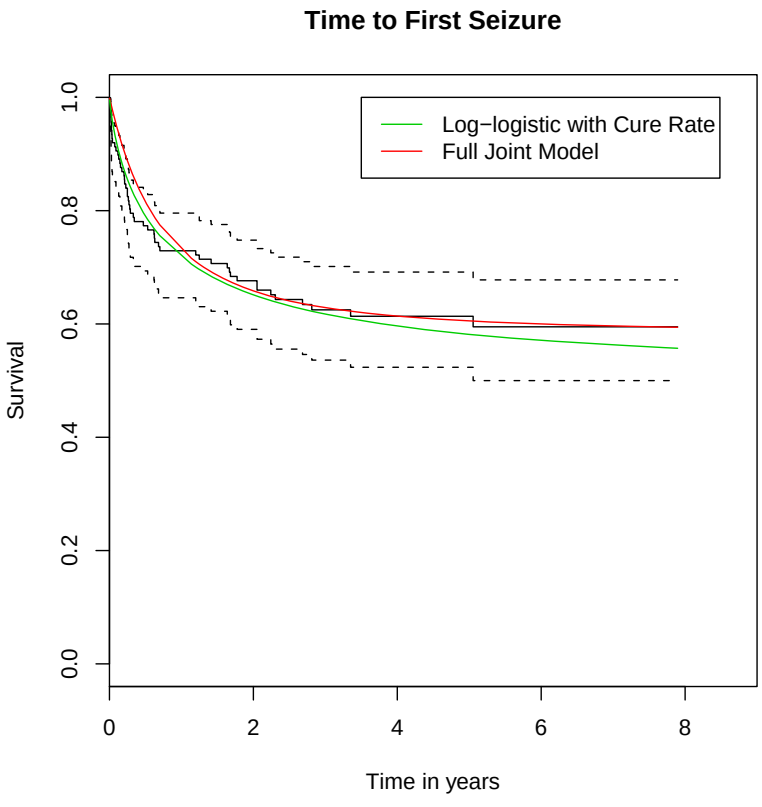
Seizure Type	$\widehat{\psi}_{2i}$ (95% C.I.) second seizure			
	Abnormal EEG			
	Immediate		Deferred	
Tonic-Clonic	3.806	(2.43,5.97)	1.554	(1.00,2.41)
2° Tonic-Clonic	1.835	(1.17,2.88)	0.870	(0.56,1.36)
Partial	2.754	(1.17,6.49)	2.047	(0.98,4.26)
	Normal EEG			
	Immediate		Deferred	
Tonic-Clonic	1.688	(1.13,2.51)	1.373	(0.93,2.02)
2° Tonic-Clonic	2.727	(1.69,4.41)	2.577	(1.67,3.97)
Partial	3.138	(1.28,7.70)	4.649	(1.63,13.27)

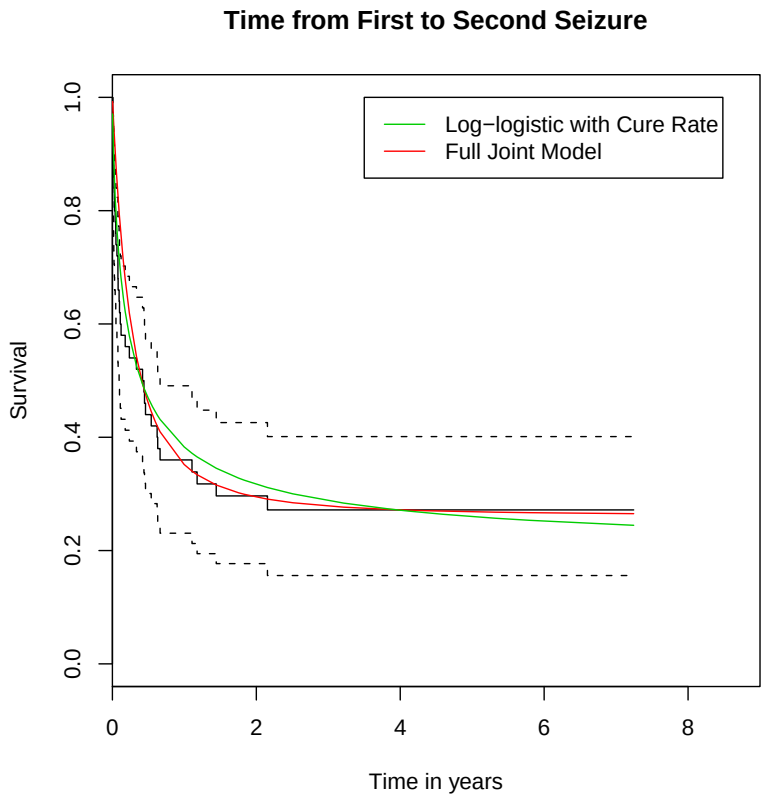
Outline

Model Comparisons

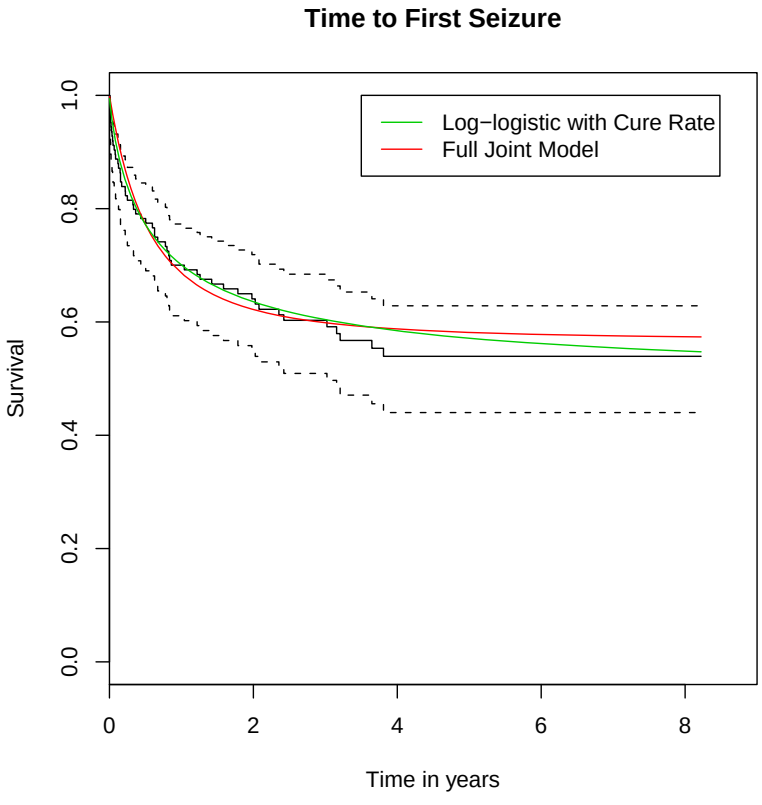
- Joint Model compared with Log-logistic cure rate model
- Kaplan-Meier estimates and fitted estimates
- Both models seem to fit data well
- Cowling et al. (2006) carried out a power analysis
- Estimates of treatment effects more precise than survival models

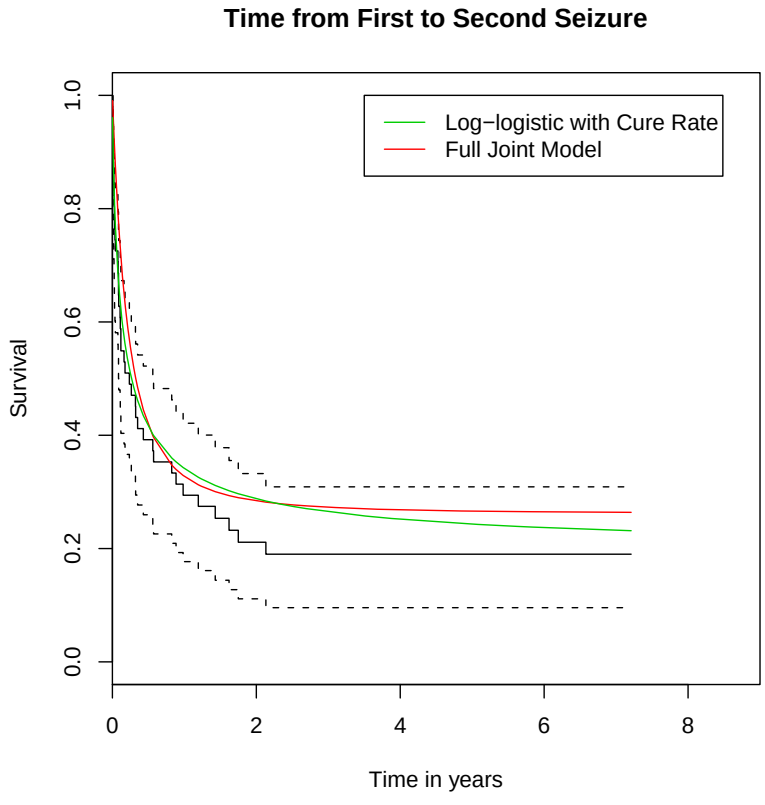
Comparison with Kaplan-Meier Curves I





Comparison with Kaplan-Meier Curves II

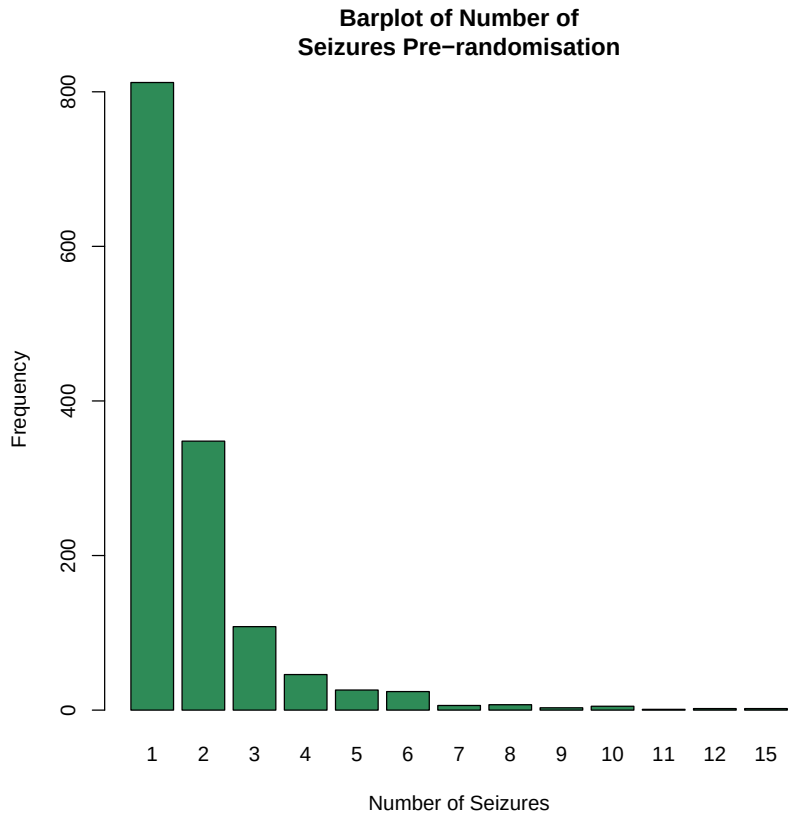




Extensions not Considered

- Zero-truncated, one-inflated Poisson Distribution
- Different AEDs
- Further post-randomisation survival times
- Analysis of long-term prognosis

Zero-Truncated, One-Inflated Poisson I



Zero-Truncated, One-Inflated Poisson II

Zero-truncated Poisson$(\lambda_i u_i \nu_i)$ distribution

$$\text{ZTP}(x_i; \lambda_i, u_i, \nu_i) = \frac{(\lambda_i u_i \nu_i)^{x_i} \exp(-\lambda_i u_i \nu_i)}{x_i!(1 - \exp(-\lambda_i u_i \nu_i))} = \frac{(\lambda_i u_i \nu_i)^{x_i}}{x_i!(\exp(\lambda_i u_i \nu_i) - 1)}.$$

One-inflated, zero-truncated Poisson distribution assumes that

$$f_X(x_i; \lambda_i, u_i, \nu_i, \pi) = \pi \mathbb{I}_{[x_i=1]} + (1 - \pi)\text{ZTP}(x_i; \lambda_i u_i \nu_i)$$

$\mathbb{I}_{[x_i=1]}$ is the indicator function taking the value 1 when $x_i = 1$ and zero otherwise

Different AEDs I

- Two randomisation forms used during the trial
- Second randomisation strategy allows comparisons between specific drugs

Different AEDs I

- Two randomisation forms used during the trial
  1. Randomisation $\rightarrow$ Drug (614 participants)
- Second randomisation strategy allows comparisons between specific drugs

Different AEDs I

- Two randomisation forms used during the trial
  1. Randomisation $\rightarrow$ Drug (614 participants)
  2. Drug $\rightarrow$ Randomisation (811 participants)
- Second randomisation strategy allows comparisons between specific drugs

Different AEDs II

- Antiepileptic drug strongly dependent on a number of baseline covariates, such as:
  - age
  - type of epilepsy
  - nature of the seizures
- Regress missing items on those influential baseline covariates we have observed
- Multiple imputation

Summary

- New modelling strategy for event counts and two survival times
- Mathematically and computationally straightforward to implement
- Extensions to ‘simple joint model considered’
- Comparisons made with standard survival techniques
- Estimates of treatment effect more precise under joint model

For Further Reading

Cook, R. J. and J. F. Lawless (2007).
The Statistical Analysis of Recurrent Events.
Statistics for Biology and Health. Springer.

Cowling, B. J., J. L. Hutton, and J. E. H. Shaw (2006).
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The Lancet 365, 2007–2013.