

First seizures - Unanswered Questions

- We know that treatment decreases risk of further seizures – but by how much and for how long?
- People's risk will vary – but what factors will determine this?
- Does early treatment effect the likelihood of chronic epilepsy – can we excluded a clinically important effect?
- If treatment has benefits does it also have harm?
- If so what might be the risk/benefit?

RANDOMIZED CONTROLLED TRIALS

- Are the least biased method of estimating a treatment effect
- If a trial is sufficiently large, the sum of known (and unknown) prognostic factors will be balanced between randomized groups
- Any difference can be confidently attributed to a treatment effect as long as the trial design and conduct are of a high quality.

Problems with RCT's

- They are expensive and difficult to conduct.
- If treatment effects are large they may not be necessary
- They won't tell you everything you want to know:
 - Rare but serious idiosyncratic reactions
 - Chronic toxicity
 - Teratogenicity

JUDGING THE QUALITY OF RCT'S

- Is it ethical?
- Is the question clearly of clinical importance?
- Is the primary outcome stated?
- Is the sample large enough to detect clinically important differences?
- Are entry criteria & methods stated and adhered to?
- Were randomization procedures robust & randomized groups comparable?
- Are all patients accounted for and do they contribute to the results?
- How applicable are the results to your clinical practice?

ISSUES THAT COMPLICATE ESTIMATES OF TREATMENT EFFECTS

- Regression to the mean
- Observer bias
 - Blinding, but is it effective?
- Patient exclusion/loss to follow-up
 - The groups analysed depart from those randomized
- Poor concealment of randomization
- In appropriate sub-group analysis



AIMS OF MESS STUDY

- Measure differences in policies
 - (immediate vs deferred treatment)
- Define prognostic factors for seizure recurrence
- Define psychosocial outcomes of policies
- Make results available in a form which allows patients to make informed decisions

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- Does early treatment effect the likelihood of chronic epilepsy – can we excluded a clinically important effect?
- If treatment has benefits does it also have harm?
- If so what might the risk/benefit?
- Compare time to first/nth seizure from randomisation
- Decide on baseline information from literature search
- Compare long-term outcomes for remission
- How to measure AEs?
- QoL measure.



CLINICAL EFFICACY OUTCOMES

- Short-term
 - Time to first seizure
 - Time to first tonic-clonic seizure
 - Time to second and fifth seizures
- Long-term
 - Time to 2 year remission
 - Terminal remission of 2 or more years 5 years after randomization

Ensuring external validity

- Are the results generally applicable?
 - Reduce exclusion criteria to a minimum
 - Collect data on non-randomized patients
 - Ensure recruited patients are well described

EXPLANATORY CLINICAL TRIALS

- Measure efficacy under optimal conditions
- Will be rigorously blinded
- Tightly defined protocol that may depart from clinical practice
- Recruit homogenous populations
- Use surrogate or intermediate end-points
- Explain mechanisms as much as outcome

REGULATORY AGENCY

- Show us it's efficacious and safe and we will give you a license
- Show us its statistically different from something
- We don't care if you construct studies biased to detect a difference
 - They can depart from clinical practice
 - They can detect differences of dubious clinical importance

Oxcarbazepine: Double-blind, randomized, placebo-controlled, monotherapy trial for partial seizures

Objective: To evaluate the efficacy and safety of oxcarbazepine in a placebo-controlled trial

Methods: A multicenter, double blind, randomized, placebo control, two-arm parallel group, monotherapy design was used to compare **oxcarbazepine administered 1200mg twice daily to placebo in hospitalized patients with refractory partial seizures**..... Patients exited the trial after **completing the 10 day double-blind treatment phase or after experiencing four partial seizures, two new onset secondarily generalized seizures, serial seizures, or status epilepticus, whichever came first.**

Results: Analysis of the **primary efficacy variable - time to meeting one of the exit criteria** - showed a statistically significant effect in favour of **oxcarbazepine (p=0.0001)**. The secondary efficacy variables - percentage of patients who met one of the exit criteria (p=0.0001) and the total partial seizure frequency per 9 days during the double-blind treatment (p=0.0001) - were also statistically significant in favour of oxcarbazepine.

Conclusion: These results demonstrate that oxcarbazepine given as monotherapy is **effective and safe for the treatment of partial seizures in this paradigm**

Schacter et al, Neurology 1999;52:732-737.

CLINICIANS & PATIENTS

- Show us how it compares with current treatment
- Reflect clinical practice
- Use *clinically important* outcomes

PRAGMATIC CLINICAL TRIALS

- Measure effectiveness in routine clinical practice
- Often unblinded but randomized
- Replicate clinical practice
- Less recruitment exclusions
- Use clinically important endpoints
- Use intent-to-treat analysis
- Often examine policies rather than treatments

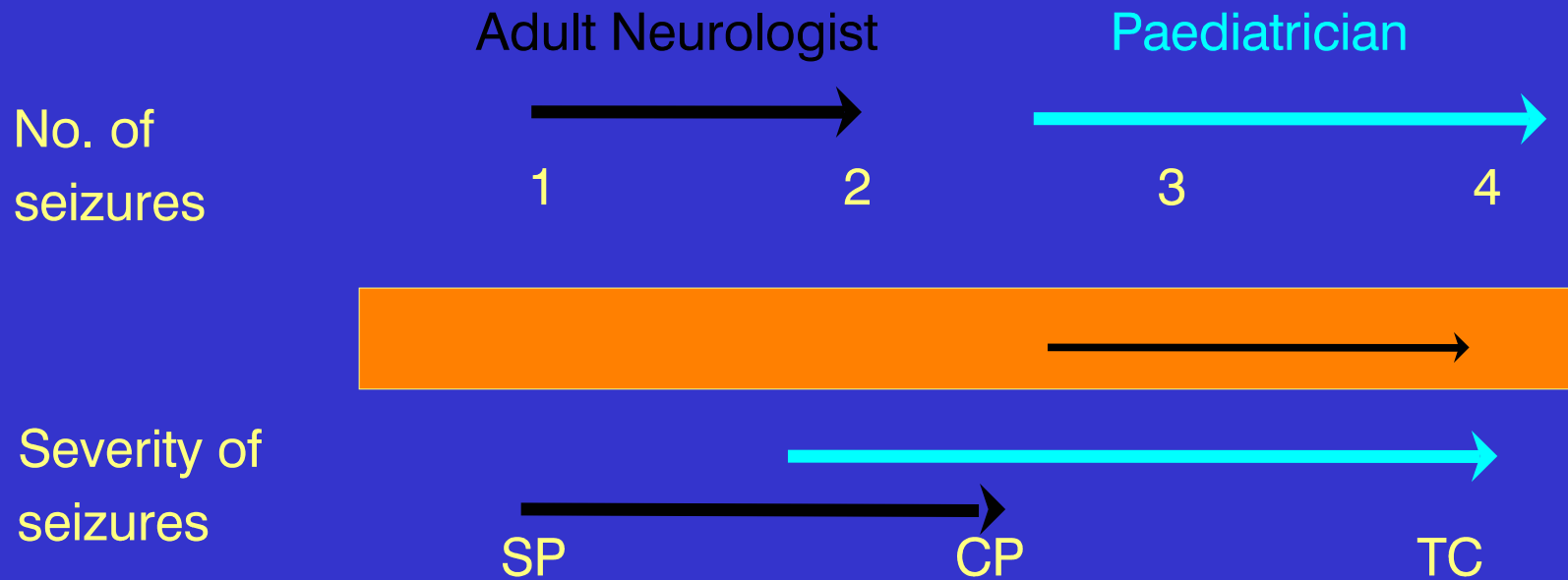
EXAMPLE OF A PRAGMATIC CLINICAL TRIAL

MRC study of early epilepsy and single seizures

- Randomization from grey-area of uncertainty
- Policies of immediate or deferred treatment
- Treatment determined by clinician
- Examines long-term remission rates

ENTRY CRITEREA IN PRAGMATIC TRIALS

The 'grey area' of uncertainty



Powering – sample size

- Varies with
 - the size of effect that it is required to detect
 - event rate in the control group
 - variance in the outcome of interest
 - level of significance (alpha) and the power that is desired (beta)
 - The desire to explore interaction between treatment effect and prognostic factors.
- We can reduce study size by :-
 - by using ineffective comparators
 - using continuous outcomes rather than rates
 - restricting entry to a very homogenous group
- All these may affect the usefulness of the data to clinical practice

We fixed the overall **type I error at 5% (two-sided)**, and to allow for multiple primary endpoints with a **Bonferroni correction we set a test-specific error of 1%**; the **type II error was fixed at 10%**. We opted for a target of 1500 patients, and in total we recruited 1443. Our **initial intention was to recruit 3000 patients to enable model testing and validation with a split-half approach**. Unfortunately, recruitment was slower than expected, and although we recruited sufficient patients for the primary analyses, the power for generation and validation of the predictive models was diminished. The trial was powered **to detect an increase from 50% to 60% or higher in the proportion of patients seizure-free at 2 years, and a reduction from 20% to 10% or lower in the proportion of patients who never attain a 2-year remission of seizures.**

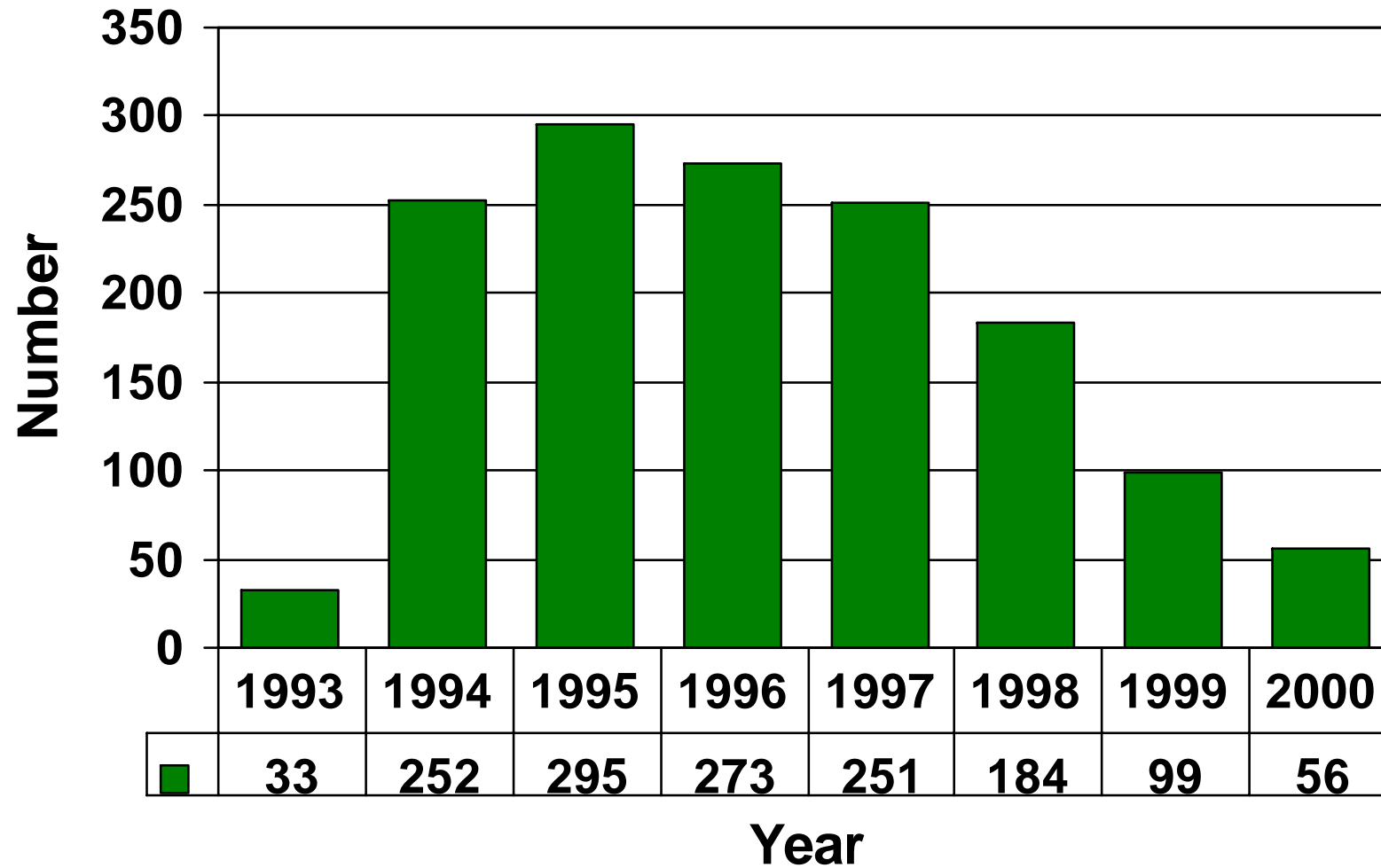
Recruitment

- Clinically important question
- Enthusiatic collaborators with a competitive spirit
- Easy to recruit and minimal effort for collaborators



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Year of recruitment



Data collection

- Minimal
 - The more data you ask for the fewer you recruit
 - Every piece of information you collect must contribute to analysis.
 - Have analysis plan before patients are recruited
 - Avoid the “wouldn’t it be interesting” temptation.

How long to collect data for?

- In a chronic condition
 - Maximise period of collection
 - The longer the collection the more clinically relevant the study
 - How long to recruit enough patients plus minimal useful period of follow-up for last recruited patient.
 - You will have varying periods of follow-up thus actuarial survival (Kaplan Meier)

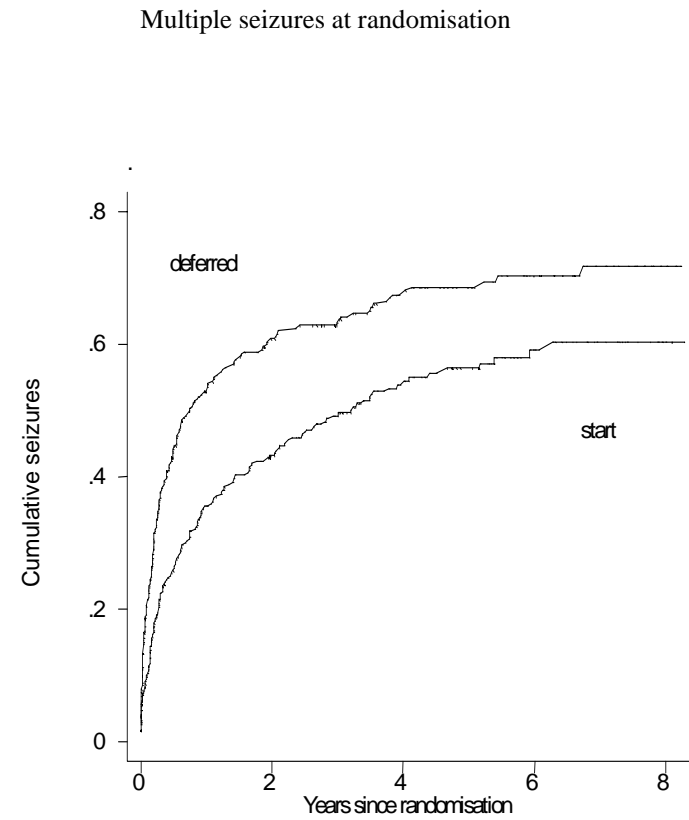
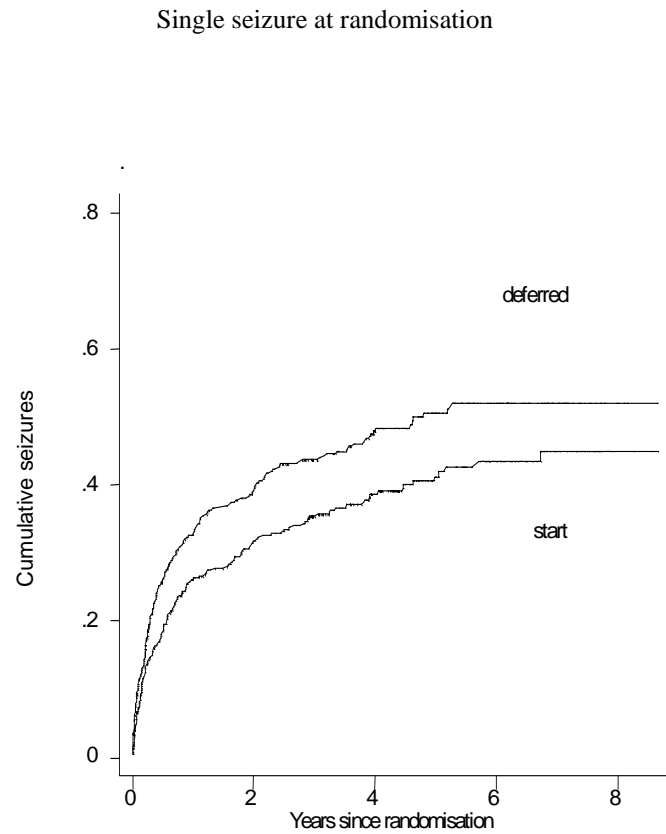


Fig. 3 Plots showing cumulative proportion of patients with first seizure after randomisation, by treatment group and stratified by number of seizures reported at randomisation

Ensuring completeness of data

- There are no easy answers!
 - A team that is totally committed to getting follow-up
 - As many different methods of obtaining information as possible
 - Ideally do the study in a country with a national health service.



Cumulative years follow-up

	Expected (years)	Actual (years)	Difference	Actual as % expected
UK data	3979	3789	190	95.2
Non UK data	2997	2522	472	84.2
Total	6976	6311	662	90.5

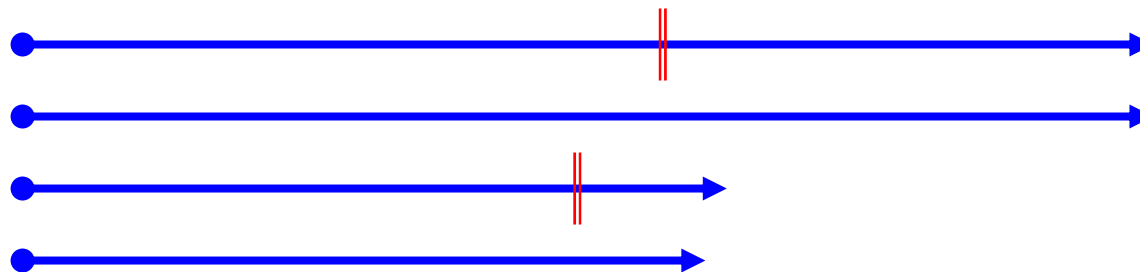
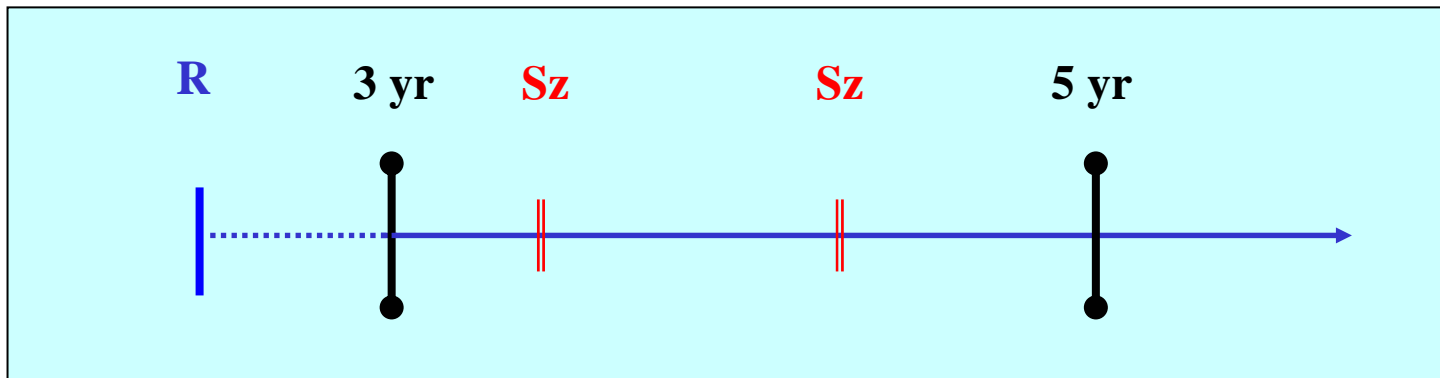


Cumulative (actuarial) Percentages achieving Two-Year Seizure Remission

Treatment	Interval from Randomisation (years)						
	2	3	4	5	6	7	8
Single Sz							
Start	69.5	84.7	91.4	93.0	95.4	95.4	95.4
Delay	61.3	80.7	90.5	91.9	94.3	96.2	96.2
Difference	8.2	4.0	0.9	1.1	1.1	-0.8	-0.8

Multi Sz							
Start	57.8	75.2	86.9	91.3	94.8	95.4	95.4
Delay	39.6	68.9	82.6	87.1	88.0	95.1	95.1
Difference	18.2	6.3	4.3	4.2	6.8	0.3	0.3

Two Year Terminal Seizure Remission at Five Years





Two year remission at 5+ years



Status	Treatment		Total (% of 1443)
	Start (% of 722)	Delay (% of 721)	
Follow-up < 3 years	189	196	385
Seizure-free in interval	201	188	389
Subtotal	390 (54)	386 (54)	774 (54)
Follow-up 5+ years			
Seizure-free	226 (68.1)	230 (68.2)	456 (68)
Seizure	106	107	213
Subtotal	332	337	669

Difference (start – delay) in %'s seizure-free (95%CL):

-0.2% (95%CL: -5.8%, 5.5%)

Predictive modelling

- Recurrence risk at 1, 3 and 5 years
- 46 Factors put into model:
 - Number of seizures before randomization
 - Interval from most recent seizure to randomization
 - Sex, Age (first seizure and entry)
 - Brain pathology
 - Neurological disorder, Abnormal neuro examination, Delayed development or learning disability
 - EEG
 - Febrile seizures.....

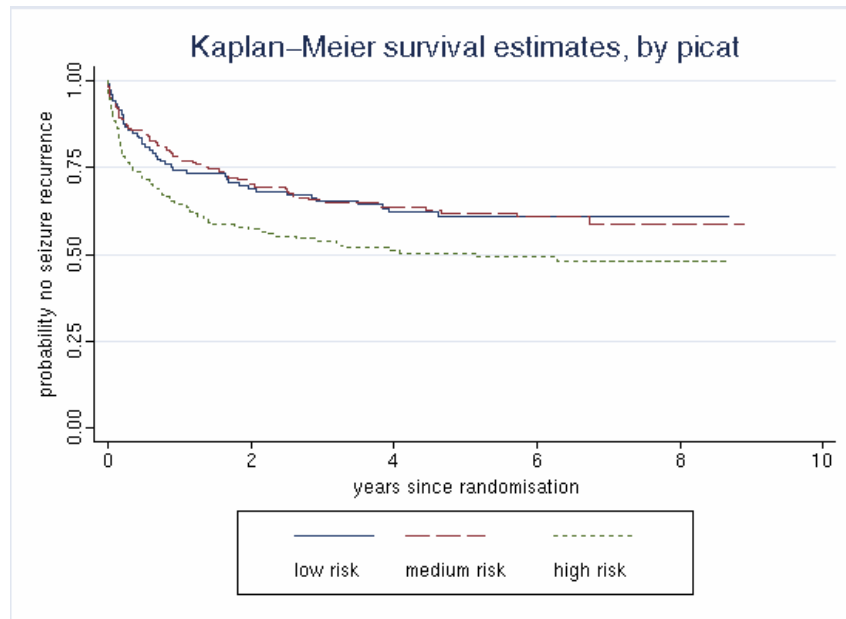
Modelling procedure

- Split sample approach
 - 60% to create model
 - 40% to test model
- Forward and backward selection
- Variables simplified
- Repeat forward and backward selection
- Model with 5 factors

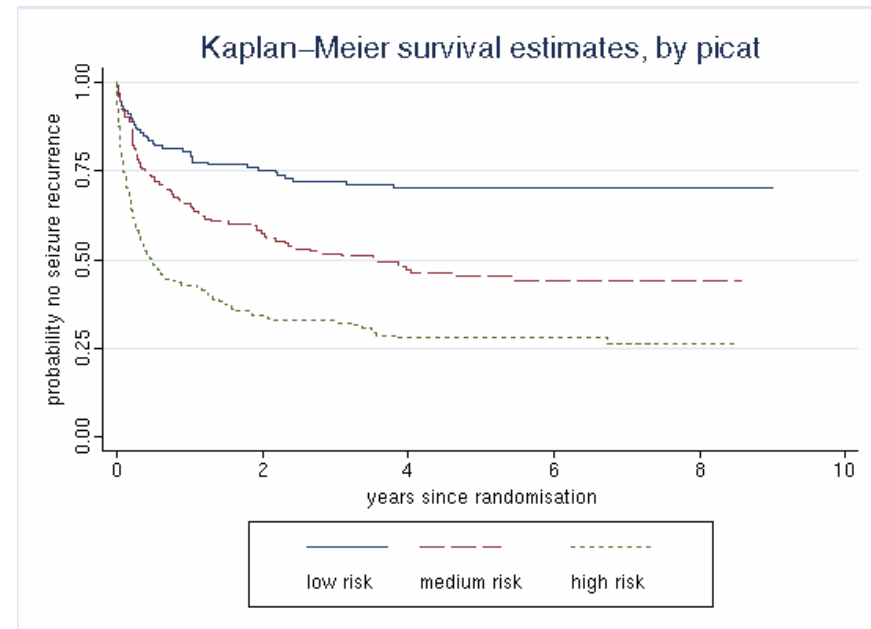
Prognostic factor	Model 1 Hazard ratio (95% CI)	Model 2 Hazard ratio (95% CI)
Neurological disorder or deficit, delayed development or learning disability	1.4 (1.1 to 1.7) (p = 0.01)	1.4 (1.1 to 1.7) (p = 0.01)
Abnormal EEG	1.5 (1.3 to 1.9) (p < 0.0005)	1.5 (1.3 to 1.9) (p < 0.0005)
No. seizures pre-randomisation (log transformation)	1.6 (1.4 to 1.7) (p < 0.0005)	1.7 (1.5 to 1.8) (p < 0.0005)
Interval between most recent seizure and randomization (years)	-	0.9 (0.8 to 1.0) (p = 0.1)
First degree relative with epilepsy	-	1.27 (0.96 to 1.70) (p = 0.1)

Risk classification	Treatment allocation	P (no seizure) at 1 year	P (no seizure) at 3 years	P (no seizure) at 5 years
Low risk	start	0.74	0.65	0.61
	delay	0.81	0.72	0.70
Medium risk	start	0.77	0.66	0.62
	delay	0.66	0.52	0.45
High risk	start	0.65	0.54	0.50
	delay	0.43	0.33	0.28

Start

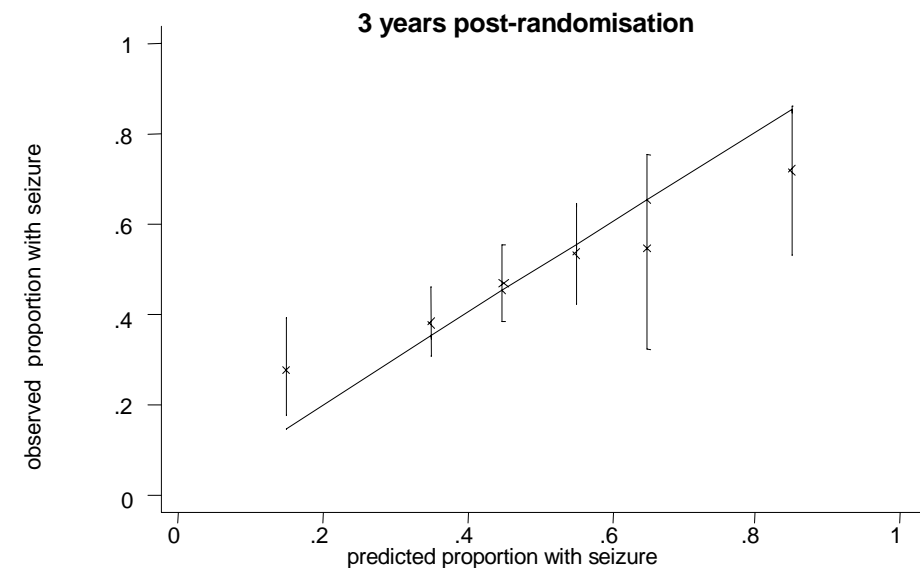
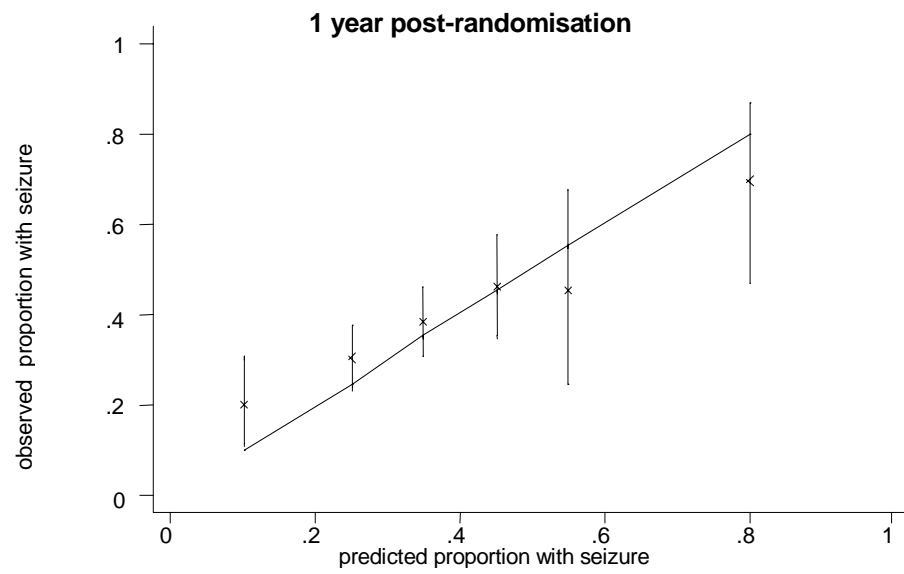


Delay



Starting value	
One seizure prior to presentation	0
Two seizures prior to presentation	1
Three or more seizures prior to presentation	2
Add if present:	
Neurological disorder/ deficit, learning disability or developmental delay	1
Abnormal EEG	1
Risk classification group for seizure recurrence*	
Low risk	0
Medium risk	1
High risk	2-4

Calibration





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