

# **Assessing the Risk of Subsequent Tonic-Clonic Seizures in Patients with a History of Simple or Complex Partial Seizures**

Rogers, J.K.\*,

Hutton, J.L.\*\*,

Marson, A.G.\*\*\*,

Chadwick, D.W\*\*\*.

\* Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, WC1E 7HT

\*\* Department of Statistics, University of Warwick, Coventry, CV4 7AL

\*\*\*Neurological Science, University of Liverpool, The Walton Centre, Lower Lane, Liverpool L9 7LJ

Address for correspondence:

Prof. David Chadwick  
The Walton Centre,  
Lower Lane,  
Liverpool L9 7LJ

email: david.chadwick@neurologynw.com  
tel:01695 574018

Key words: Epilepsy, partial seizures, tonic-clonic seizures, risk factors, recurrence rates, antiepileptic drug treatment.

Word Count: 3337

***This is the peer reviewed version of the following article: J.K. Rogers, J.L. Hutton, A.G. Marson, and D.W. Chadwick. Assessing the risk of subsequent tonic-clonic seizures in patients with a history of minor seizures. Journal of Neurology Neurosurgery and Psychiatry 2012; 83:803-809, which has been published in final form at doi.org/10.1136/jnnp-2011-300917.***

## **Abstract**

**Background:** Patients who present with only simple or complex partial seizures have a poorly documented prognosis. Treatment may be advocated to prevent future secondary generalised seizures, reduce the frequency of further simple or complex partial seizures, or a combination of both.

**Methods:** We carried out a full statistical analysis on 1334 patients. The outcomes measured were post-randomisation times to first seizure of any type and first tonic-clonic seizure. We adopted methodology that accounted for individuals' underlying pre-randomisation seizure counts and allowed for the possibility that there may be a proportion of the sample that won't experience post-randomisation seizure recurrence.

**Results:** 103 subjects randomised to the MESS (Multicentre Study of Early Epilepsy and Single Seizures) study had only partial seizures at randomisation. Only 17 of these had a tonic-clonic seizure during follow-up. The presence of an abnormal EEG at randomisation influenced this risk: an estimated 23% of those with EEG abnormality were at risk of tonic-clonic seizures during follow-up, compared to 16% of those with a normal EEG. The group did, however, continue to have partial seizures during follow-up, and modelling showed that the impact of treatment on these seizures was significantly less than the effects of treatment on the frequency of tonic-clonic seizures in those patients with such pre-randomisation seizures.

**Conclusion:** Patients presenting with a history of only partial seizures are at low risk of subsequent tonic-clonic seizures in the period of time to which therapeutic decisions are relevant. The effects of the antiepileptic drugs used in the MESS study are greater for tonic-clonic seizures than they are for partial seizures.

## Introduction

One of the most important decisions for a person with newly diagnosed epileptic seizures will be whether to start treatment with an antiepileptic drug (AED). A risk-benefit assessment considers the risks and costs associated with AEDs on one hand and the benefits of AED treatment on the other. The benefits of AED treatment will be the potential reduction in short-term recurrence of seizures and the long-term outcomes of epilepsy, whilst the risks include common, usually dose related, adverse effects, as well as rare, but potentially life threatening events idiosyncratic events such as epidermal necrolysis.

There is a considerable body of evidence about the risk of further seizures following a first tonic-clonic seizure. This topic was the subject of one of the first, and most impressive, systematic reviews in epilepsy [1]. Ultimately, of those with a single, untreated seizure, 50% will have further seizures [2]. These are however, average risks that will vary with a number of factors, which include the presence or absence of underlying brain disease, of which seizures and epilepsy may be symptomatic, and an abnormal EEG.

Existing literature on first seizures focuses on the risk of future tonic-clonic seizures in patients who have presented with a tonic-clonic seizure[1]. For those patients who have a diagnosis of epilepsy, but have never experienced a tonic-clonic seizure, information about the risk of future tonic-clonic seizures may be the most relevant. These individuals may well have lived for some time with recurrent seizures that are either partial (simple or complex), or generalised absence or myoclonic seizures, and may be willing to continue to do so, without AED treatment. If it were to be shown that the risk of tonic-clonic seizures for these individuals is low, individuals may consider the potential effect of AED treatment on the rate at which future less severe seizures occur. For these individuals, there is little available evidence to inform decision-making.

Clinicians will recognise that in patients presenting with a first tonic-clonic seizure, other seizures may well have occurred for some considerable time, as emphasised by King et al [3]. Indeed, direct questioning to elicit a history of other seizures is an important step in classifying seizures and epilepsy syndromes. However, clinical experience will inevitably be biased towards an impression that most patients will sustain tonic-clonic seizures eventually, as patients with tonic-clonic seizures are more likely to see clinicians.

The MRC Multicentre Trial of Early Epilepsy and Single Seizures (MESS) was a randomized controlled trial that compared the policies of immediate and deferred treatment for patients presenting with a single seizure or early epilepsy [4]. Because of its broad entry criteria, MESS recruited patients

presenting with a number of different seizure types pre-randomisation. In this paper we explore the times to first seizure of any type and to first tonic-clonic seizure in patients without tonic-clonic seizures pre-randomisation and compare these with estimates for those who presented with at least one tonic-clonic seizure. We have used new statistical methodology to model underlying seizure frequency in our patients and the effects of treatments on those rates, focusing on the potentially differing impacts of treatment on the frequency of simple and complex partial seizures compared to tonic-clonic treatments.

## **Methods**

A detailed description of methods and primary results of the MESS study is given in Marson et al. [4]. The study was approved by the appropriate multicentre ethics committee. MESS randomised 1443 patients to either immediate or deferred treatment, with the inclusion criteria being: aged at least one month, having a suitably documented history of at least one clinically definite, unprovoked epileptic seizure and both the clinician and patient being uncertain as to whether treatment with AEDs should commence. This allowed entry of subjects with single seizures, subjects with infrequent seizures and patients with more frequent seizures with less severe symptomatology. Thus, MESS randomised people presenting with tonic-clonic seizures pre-randomisation (which included primary and secondary generalised seizures) and with seizures that were simple partial, complex partial, or generalised absence and myoclonic seizures. Those patients randomised to the deferred treatment group started treatment when both clinician and patient agreed that treatment was necessary, which primarily occurred following further seizures. MESS was a pragmatic trial, so that subsequent choices of antiepileptic drug, dose and duration of treatment were in line with the clinicians' usual practice. Patients' seizures and epilepsy syndromes were classified, pre-randomisation, by international criteria [5-7]. Because few seizures had occurred relatively few subjects had any syndromic classification and the clinical descriptions are therefore dependent on seizure classification.

For this paper, six seizure categories are used (Table 1), that differ from those used in previous analyses. The 'tonic-clonic only' group were patients with a history of tonic-clonic seizures without any other recorded seizures. This group included patients with primary generalized seizures and seizures where the clinician could not confidently classify seizures as secondary generalized. Other categories included patients with: definite secondary generalised tonic-clonic seizures, with or without either simple partial or complex partial seizures ('tonic-clonic with partial'); tonic-clonic seizures and absence or myoclonic ('tonic-clonic with generalised seizures'); simple partial or complex partial seizures ('partial seizures'); absence or myoclonic seizures. The final group included

unclassified but definite seizures ('other seizures'). For the sake of convenience and brevity, in this paper we have used the term 'minor' to describe seizures occurring in the population that were not generalised tonic clonic or secondary generalised seizures. This would include absence, myoclonus and simple and complex partial seizures. We would emphasise that for many people with epilepsy, the occurrence of such seizures will be a cause of significant disability. However, subjects willing to accept randomisation to a policy of no treatment would have been less likely to be experiencing seizures causing significant disability. For this reason the term 'minor' may be more acceptable.

The information collected at randomisation included imaging and EEG. Any EEG may have been a standard awake inter-ictal recording or a sleep recording. UK practice at the time of the study would mean that sleep recording would have been uncommon.

The MESS data includes a pre-randomisation seizure count, with the associated number of days over which these seizures were observed, and post-randomisation the times to first seizure of any type and first tonic-clonic seizure. Time to first seizure is an internationally agreed outcome in epilepsy trials [8, 9].

Exploratory analysis was carried out on 1425 individuals; 18 were removed due to missing information, assumed missing at random. A further five patients with incomplete information on pre-randomisation seizures were excluded from the final statistical modelling. Each of the groups: 'tonic-clonic with generalised', 'myoclonic and absence' contained individuals presenting with absence or myoclonic seizures pre-randomisation. Seizure frequency for these seizure types is typically much higher than other seizure types, so these groups were excluded from the statistical modelling. Analysing all the groups together may have given misleading results and these groups are too small to analyse separately. Statistical models were fitted for those individuals presenting with 'tonic-clonic only', 'tonic-clonic with partial' and 'partial', with a resulting sample size of 1334.

The pre-randomisation period at risk of seizures (the time from first seizure to randomisation) is essential in the estimation of pre-randomisation seizure rates. Of the 1425 individuals included in the exploratory analysis, 812 presented with only a single seizure pre-randomisation. For these individuals the period of time from first seizure to randomisation may be inaccurately small, and these imprecise estimates of their associated underlying seizure rates would result in an overestimation of any seizure reductions. We subsequently adjusted the data, so that the minimum period of time over which pre-randomisation seizures were observed was 182 days (6 months). This definition was subject to a sensitivity analysis. This approach has the virtue of recognising a clinical assumption that except when seizures are clearly provoked (for instance acute symptomatic seizures

due to alcohol withdrawal), the first seizure may not coincide with the onset of a significant susceptibility to seizures, merely the day upon which a number of poorly understood factors combined with an underlying susceptibility to result in a seizure.

Previous analyses of the MESS times to first seizure and first tonic-clonic seizure used a Cox proportional-hazards model, with the pre-randomisation seizure information as a baseline covariate. However, if the proportional hazards assumption does not hold, an alternative to this approach, which fits our data well, is accelerated failure time models, which assume that the actual times to events are proportional.

We jointly modelled the pre-randomisation seizure counts and post-randomisation survival times [11]. These methods have been modified to allow for the inclusion of cure rates [12]. Berg and Shinnar [1] noted that, on average, around 50% of people do not experience seizure recurrence after a single seizure. As 57% of the 1425 individuals presented only a single seizure pre-randomisation, it is reasonable to expect that a substantial proportion of the individuals included in the MESS trial would never have a seizure post-randomisation, regardless of the length of follow-up. If data include a proportion of patients that are not at risk of seizure recurrence, a model that ignores this may result in underestimates of the post-randomisation seizure rates [13].

We assume that both the pre-randomisation seizure counts and post-randomisation survival times are predicted by (unobserved) seizure rates. Each patient has an underlying constant seizure rate that depends on important factors. A proportion of those randomised are assumed to be not at risk of seizure recurrence; for those who are at risk, the post-randomisation seizure rates will be modified relative to the baseline seizure rate. A greater reduction in the seizure rate results in a longer time to seizure post-randomisation, indicating a more effective therapy. Further details of this model can be found in the Appendix.

## **Results**

### ***Exploratory Analysis***

Table 1 shows the clinical features for 1425 people, stratified by seizure type pre-randomisation and the treatment policy allocated. Most (88%) of the 1425 participants presented with at least one tonic-clonic seizure pre-randomisation, but 103 presented with partial seizures only pre-randomisation.

We observe that there is a substantial proportion of patients that do not have any seizures during follow-up. We also see that for those patients who present with tonic-clonic seizures pre-

randomisation and have subsequent seizures post-randomisation, it is likely that at least one of their post-randomisation seizures will be tonic-clonic. This is not true for those presenting with partial seizures only pre-randomisation.

Table 2 gives the percentages of patients presenting with any seizure and with a tonic-clonic seizure at 6 months, 1, 2, 3 and 5 years from randomisation. At one year post-randomisation, 342 of those with tonic-clonic seizures pre-randomisation, and 8 of those who presented with partial seizures only, had experienced at least one tonic-clonic seizure. Hence those with tonic-clonic seizures pre-randomisation were more likely to have tonic-clonic seizures post-randomisation, compared to those with only partial seizures pre-randomisation (1 year relative risk: 3.48 [95% CI (1.78,6.80)]). This finding is mirrored by the Kaplan-Meier plots shown in Figure 1.

	Tonic-Clonic Only**		Tonic-Clonic with Partial		Tonic-Clonic with Gen		Partial Seizures		Myoclonic & Absence		Other Seizures	
	Imm	Def	Imm	Def	Imm	Def	Imm	Def	Imm	Def	Imm	Def
Number at randomisation	375	406	239	215	17	15	51	52	9	8	21	17
Number with single seizure pre-rand	253	263	116	115	0	0	19	18	3	2	13	10
Number with multiple seizures post-rand	122	143	123	100	17	15	32	34	6	6	8	7
Number with at least one seizure post-rand	155	204	106	117	9	13	29	32	5	4	7	10
Number with at least one T-C* post-rand	138	187	78	98	7	9	9	8	3	1	5	7
Percentage first seizure is T-C (s.e.)	81.9 (3.1)	87.8 (2.3)	58.5 (4.7)	71.8 (4.1)	66.7 (15.7)	46.2 (13.5)	6.9 (5.7)	18.8 (6.9)	40.0 (16.6)	0 (15.3)	57.1 (15.0)	50.0 (13.4)
Percentage having any seizure who have a T-C (s.e.)	89.0 (2.6)	91.7 (2.0)	73.6 (4.3)	83.8 (3.4)	77.8 (12.8)	69.2 (11.6)	31.0 (8.2)	25.0 (7.5)	60.0 (16.6)	25 (17.1)	71.4 (14.5)	70.0 (12.8)
Percentage with abnormal EEG (s.e.)	41.6 (2.5)	40.9 (2.4)	40.6 (3.2)	40.9 (3.3)	58.8 (10.8)	60.0 (11.3)	68.6 (6.3)	61.5 (6.5)	100.0 (10.0)	37.5 (14.2)	38.1 (9.8)	41.2 (10.8)

**Table 1: Clinical features for the 1425 individuals included in the exploratory analysis.**

\*Tonic-Clonic. \*\*Tonic-clonic seizures either generalised in onset or not definitely focal onset. Imm – immediate treatment. Def deferred treatment.

For those with at least one tonic-clonic seizure pre-randomisation, deferred treatment and an abnormal EEG increased the risk of a further tonic-clonic seizure (1 year relative risks 1.45 [95% CI

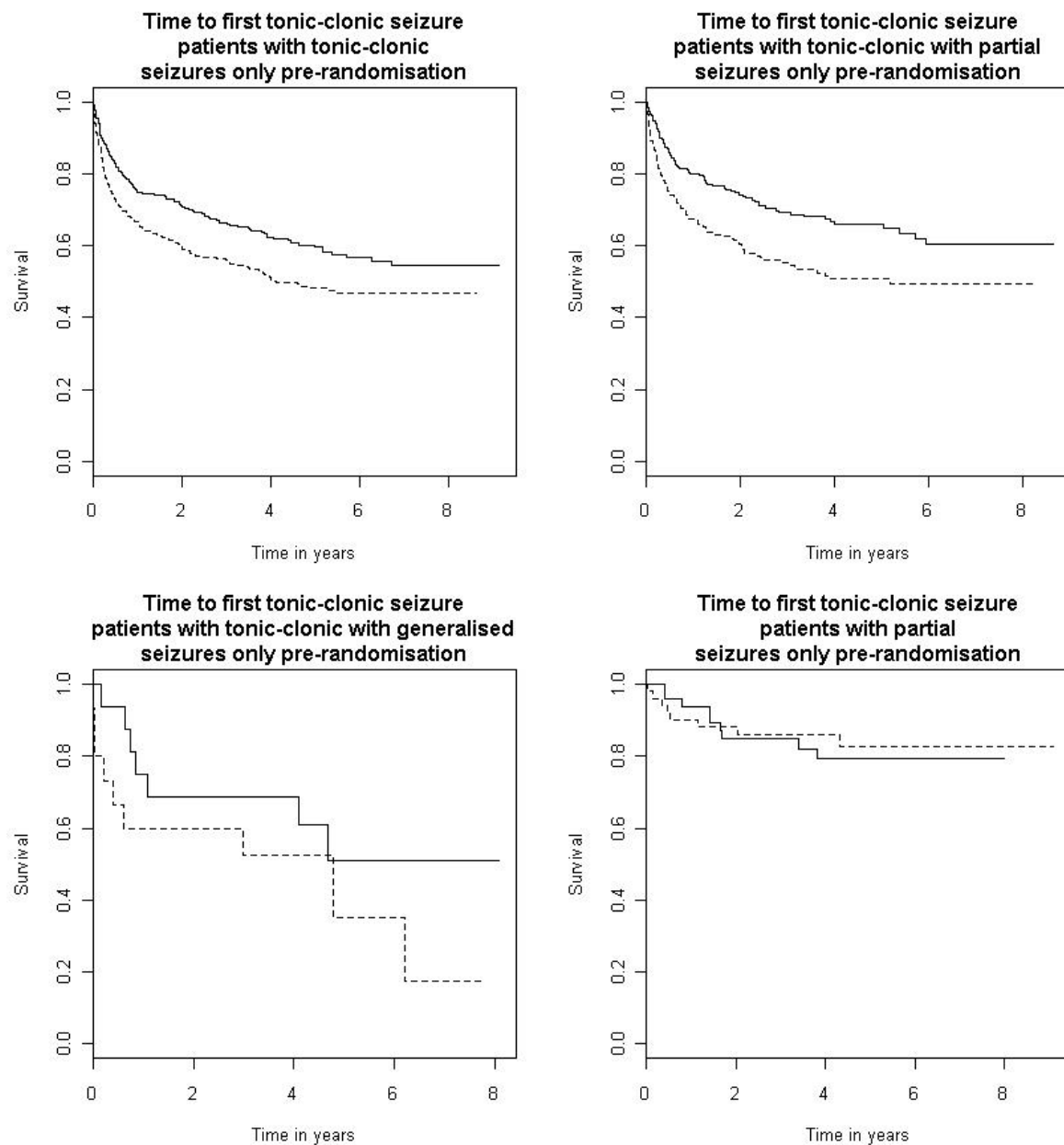
(1.20,1.74)] and 1.24 [95% CI (1.03,1.48)] respectively). For those with only partial seizures pre-randomisation the 1 year relative risks were 1.64 [95% CI (0.41,6.49)] and 1.61 [95% CI (0.34,7.58)] respectively. Although the estimated relative risks are larger than observed for those with tonic-clonic seizures, the confidence intervals are larger, owing to the lack of power, and the results are not statistically significant.

	Tonic-Clonic only		Tonic-Clonic with Partial		Tonic-Clonic with Gen		Partial Seizures		Myoclonic & Absence		Other Seizures	
	Imm	Def	Imm	Def	Imm	Def	Imm	Def	Imm	Def	Imm	Def
Percentage with any seizure at:												
6 months	19.3	29.0	22.4	35.5	18.4	60.0	29.6	46.6	44.4	53.1	21.6	31.2
1 year	27.6	36.4	30.2	42.8	37.3	73.3	44.7	52.7	55.6	53.1	27.2	56.2
2 years	34.0	44.3	36.8	49.4	43.5	80.0	56.2	57.0	55.6	53.1	27.2	62.5
3 years	38.1	48.2	42.4	53.4	43.5	80.0	58.6	59.3	55.6	53.1	43.4	62.5
5 years	46.4	56.1	46.4	57.8	58.8	80.0	61.2	63.8	55.6	53.1	43.4	62.5
Percentage with T-C seizure at:												
6 months	17.1	27.2	14.3	25.6	6.2	33.3	4.1	7.8	22.2	16.7	11.1	12.5
1 year	25.1	33.5	19.9	32.4	24.9	40.0	6.3	9.7	33.3	16.7	16.7	37.5
2 years	29.3	40.6	25.8	39.6	31.2	40.0	15.2	11.8	33.3	16.7	16.7	43.8
3 years	33.8	44.0	30.7	44.6	31.2	47.5	15.2	13.9	33.3	16.7	31.8	43.8
5 years	40.4	51.9	34.1	49.2	49.1	65.0	20.7	17.2	33.3	16.7	31.8	43.8

**Table 2: Kaplan-Meier estimates of survival for different seizure types and treatment policy.**

Imm – immediate treatment. Def deferred treatment.





**Figure 1: Kaplan-Meier plots for first tonic-clonic seizure, stratified by treatment.**  
**Immediate: —————, Deferred: - - - - -.**

### **Statistical Modelling**

The estimated regression coefficients are given in the Appendix. These regression coefficients can be used to calculate estimates of the pre-randomisation seizure rates; the probabilities associated with having seizures during follow-up; and the subsequent change in seizure rates post-randomisation for those at risk of seizure recurrence. No statistically significant gender effect was found for the baseline seizure rate, cure rates or seizure rate modifiers.

Underlying seizure rates varied substantially with pre-randomisation seizure types and age, with younger individuals typically having a higher baseline rate. Patients presenting with partial seizures

only pre-randomisation, typically have the highest seizure rate, presenting with a seizure once approximately every two months. Those with tonic-clonic seizures only pre-randomisation can expect to have the lowest seizure rate, presenting with around two seizures a year, whilst those with secondary generalised tonic-clonic seizures can expect to present with three seizures a year.

Treatment policy and age were not important in determining whether a person is at risk of further seizures post-randomisation (within eight years), but pre-randomisation seizure types and EEG outcome were. The estimated probabilities of having any seizure post-randomisation are 45-80% (Table 3 & Figure 2). For those with at least one tonic-clonic seizure pre-randomisation, those with an abnormal EEG have higher expected risk of a post-randomisation seizure, than those with a normal EEG, but no statistically significant difference is apparent for the partial seizure group.

Estimated percentage having any seizure during 8 year follow-up (95% CI)				
	Abnormal EEG		Normal EEG	
Tonic-clonic	65	(56,72)	51	(45,56)
2° Tonic-clonic	76	(67,84)	45	(38,52)
Partial	61	(48,73)	72	(52,86)
Estimated percentage having a tonic-clonic seizure during 8 year follow-up (95% CI)				
	Abnormal EEG		Normal EEG	
Tonic-clonic	59	(52,66)	47	(42,52)
2° Tonic-clonic	55	(47,62)	43	(36,51)
Partial	23	(14,36)	16	(9,27)

**Table 3: Estimated percentages having any seizure, or a tonic-clonic seizure, during 8 year follow-up, by seizure type and EEG outcome.**

Patients who presented with partial seizures only pre-randomisation are at the lowest risk of having a tonic-clonic seizure within eight years of randomisation, with estimated percentages of 23% and 16% for those with abnormal and normal EEGs respectively (Table 3). For those who had presented with at least one tonic-clonic seizure pre-randomisation, the associated risks of further tonic-clonic seizures are around 40-60%. Those with an abnormal EEG have higher expected risks of a tonic-clonic seizure post-randomisation than those with a normal EEG, but this difference is only statistically significant for the 'tonic-clonic only' group.

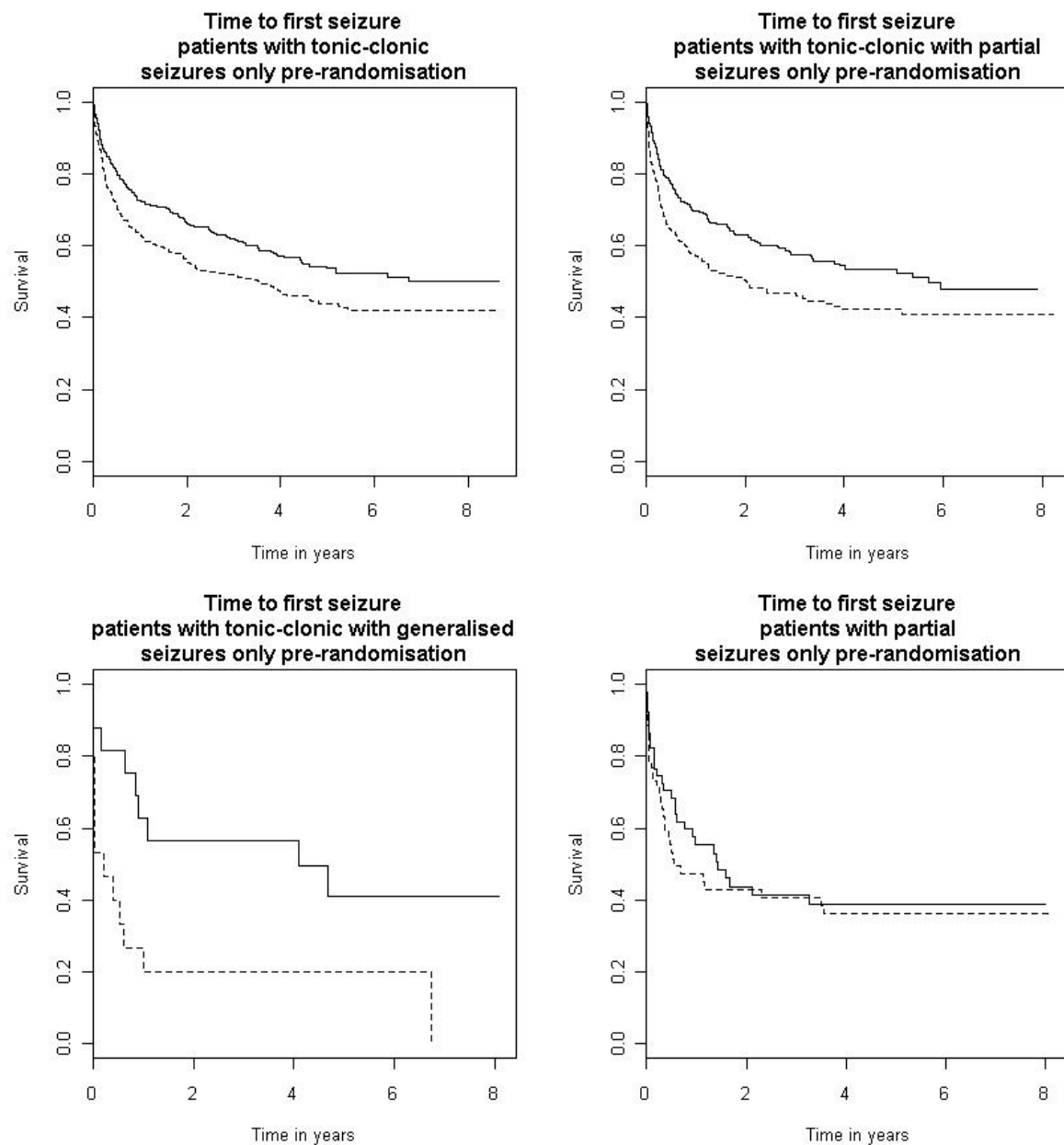
Additionally, for those presenting with tonic-clonic seizures only pre-randomisation, their probability of having any seizure post-randomisation is only slightly greater than their probability of having a tonic-clonic seizure post-randomisation. This suggests that if these individuals do have a seizure post-randomisation, we can expect this seizure to be tonic-clonic.

Although treatment policy was not important in determining whether an individual has a further seizure of any type, or a tonic-clonic seizure post-randomisation, it does effect the expected time to seizures for those patients at risk. The effect of randomisation to immediate or deferred treatment in those patients at risk of post-randomisation seizures, sub-grouped by EEG is summarised in Table 4. To illustrate, consider an individual presenting with partial seizures only pre-randomisation, an abnormal EEG, and allocated to immediate treatment; they would expect to have a post-randomisation seizure rate that is 43% of their pre-randomisation seizure rate. Note that all post-randomisation seizure rates are reduced, suggesting a regression to the mean effect.

Predicted seizure rate post-randomisation, as a percentage of pre-randomisation seizure rate (95%CI) (any seizure)						
	Abnormal EEG				Normal EEG	
	Imm		Def		Imm	Def
Tonic-clonic	19	(12,30)	64	(48,86)	48	(35,66)
2° Tonic-clonic	18	(13,27)	76	(55,106)	36	(23,55)
Partial	43	(23,78)	68	(39,117)	46	(23,91)
Predicted seizure rate post-randomisation, as a percentage of pre-randomisation seizure rate (95%CI) (tonic-clonic seizure)						
	Abnormal EEG				Normal EEG	
	Imm		Def		Imm	Def
Tonic-clonic	16	(10,25)	64	(46,87)	45	(32,63)
2° Tonic-clonic	21	(13,35)	70	(49,100)	24	(14,40)
Partial	14	(4,47)	26	(9,76)	9	(3,31)

**Table 4: Predicted seizure rate post-randomisation, as a percentage of pre-randomisation seizure rate, by seizure type, EEG outcome and treatment policy (age fixed at 30).**

The impact of immediate treatment on the expected time to next seizure of any type is considerable for the tonic-clonic and secondary tonic-clonic groups, particularly where the EEG is abnormal. However, immediate treatment has little obvious effect on expected seizure rates for the partial group, as would be expected from the Kaplan-Meier plots (Figure 2).



**Figure 2: Kaplan-Meier plots for first seizure of any type, stratified by treatment.**  
**Immediate:**—————, **Deferred:** -----

Expected changes in post-randomisation tonic-clonic seizure frequency is also expressed as a percentage of the rate of all seizures pre-randomisation (Table 4). Here an individual presenting with partial seizures only pre-randomisation, an abnormal EEG, and allocated to immediate treatment would expect to have a post-randomisation tonic-clonic seizure rate that is 14% of their pre-randomisation partial seizure rate. Once more, a marked effect of treatment policy is seen in the tonic-clonic and secondary tonic-clonic groups. For the partial minor group there is once again no indication of significant benefit from immediate treatment.

The expected post-randomisation seizure rates can be used to give estimates of the expected number of months to next seizure. Table 5 gives the expected number of months to the first post-randomisation seizure of any type and first post-randomisation tonic-clonic seizure.

Post-randomisation expected number of months to next seizure (any seizure)						
	Abnormal EEG				Normal EEG	
	Imm		Def		Imm	Def
Tonic-clonic	32	(20,49)	9	(7,2)	12	(9,17)
2° Tonic-clonic	22	(15,32)	5	(4,7)	11	(7,18)
Partial	5	(3,9)	3	(2,5)	4	(2,9)
Post-randomisation expected number of months to next seizure (tonic-clonic seizure)						
	Abnormal EEG				Normal EEG	
	Imm		Def		Imm	Def
Tonic-clonic	37	(24,62)	9	(7,13)	13	(10,18)
2° Tonic-clonic	19	(12,32)	6	(4,8)	18	(10,29)
Partial	14	(4,48)	8	(3,23)	22	(7,75)

**Table 5: Predicted number of days to next seizure (for those that are susceptible to seizure recurrence, by seizure type, EEG outcome and treatment policy (age fixed at 30)).**

We can see that a person presenting with tonic-clonic seizures pre-randomisation and an abnormal EEG, who has further seizures, would expect to have a seizure within 10 months without treatment, and at around three years with immediate treatment. We also observe that these seizures are likely to be tonic-clonic seizures. Additionally, for those presenting with partial seizures pre-randomisation, we see that the expected number of months to next seizure of any type is much shorter than the expected number of months to a tonic-clonic seizure.

## Discussion

This paper has examined the effects of immediate versus deferred treatment on times to first post-randomisation seizure of any type and first post-randomisation tonic-clonic seizure. The effect of pre-randomisation seizure type on underlying seizure rates, risks of post-randomisation seizure recurrence, and post-randomisation seizure rate modifiers, has also been investigated.

The seizure type groups that contained individuals presenting with absence and myoclonic seizures pre-randomisation were excluded from the statistical modelling. These groups are too small to analyse separately, but those individuals presenting with absence and myoclonic seizures typically have a disproportionate seizure frequency to the other seizure groups. Insufficient numbers of patients who had only minor generalised seizures (absence and myoclonic) were included in the MESS data for any valid conclusions to be drawn. Examination of the Kaplan-Meier plots does not

provide any indication that this group's risk of tonic-clonic seizures is markedly different from those patients in whom there was a history of tonic-clonic seizures before randomisation.

There were however, a sufficient number of subjects included that had a history of only partial seizures prior to randomisation. The probabilities of future secondary generalised tonic-clonic seizures and the effect of treatment policy on the time to first tonic-clonic seizure for those susceptible, for these individuals, has been explored. This group was at low risk of tonic-clonic seizures and it was further concluded that an abnormal EEG was not significant in determining the probability of secondary generalised tonic-clonic seizures. As would be expected, immediate treatment with AEDs had little benefit in reducing the subsequent incidence of secondary generalised tonic-clonic seizures, for those that were susceptible. For this reason, the main issue to be considered in this group of patients will be the effect of immediate treatment on the frequency of their other simple and complex partial seizures. When this is examined, changes in seizure rates post-randomisation with immediate treatment are much less than those seen in groups of patients with tonic-clonic seizures pre-randomisation, an observation that is in keeping with the hypothesis that partial seizures are generally more resistant to AEDs than tonic-clonic seizures, be these generalised at onset or secondarily generalised.

This is a finding that may have some regulatory implications. There has been some debate about the licensing of new AEDs. These are brought to market through trials that compare add-on drugs with placebos in subjects with a history of pharmacologically resistant partial seizures [14]. The key outcomes will be the reduction in seizure frequency compared to placebo, but the patients included are likely to have many more simple or complex partial seizures than secondary generalised seizures. Thus, it can be questioned whether such trials provide reasonable evidence of effectiveness against secondary generalised seizures (they usually lack the power to do so). Our data, from a different population of patients with partial seizures, may suggest that at least for the drugs chosen by clinicians in the MESS study (carbamazepine and to a lesser degree valproate for patients with partial with or without secondary generalised seizures) the effects on seizure frequency are greater for secondary generalised tonic-clonic seizures than partial seizures. Thus a drug that is effective in reducing partial seizures is unlikely to lack effectiveness in reducing secondary generalised tonic-clonic seizures.

The MESS study and others has already drawn attention to the importance of EEG abnormality in prediction of future risk of seizures. This is evident once more in this treatment of the data. However, it is important to recognise that it is the presence of any abnormality that predicts outcome and that further refinement of the abnormality (epileptiform versus other abnormalities) confers little if any

additional precision. It should be recognised that the great majority of EEG's for patients in the study were standard non-sleep recordings and that sleep recordings may have provided information of greater prognostic significance.

MESS was not a population based study, but was a trial comparing the policies of immediate and deferred AED treatment. Patients selected for entry were those where both clinician and patients were uncertain about the need for AED treatment, thus data from MESS may not immediately generalise to the patients for whom there is no 'grey area' of certainty about the need for treatment, that would include patients with very frequent or intrusive partial seizures. It is difficult to judge whether MESS will have overestimated or underestimated seizure recurrence risks, as patients with a higher risk of recurrence, where patient and clinician were certain that treatment was required, will not have entered the study, while similarly patients at a lower risk of recurrence, where patient and clinician were certain that treatment was not needed, would not have entered the study. The study was also pragmatic reflecting true clinical practice at the time, including the potential for misdiagnosis inherent in the management of epilepsy particularly when few events had occurred. Further there was no systematic screening for poor adherence beyond that routinely undertaken by collaborators. The choice of drug was not randomly allocated, but that judged optimal by collaborators. In contrast it does have the strength of reflecting true clinical practice rather than any atypical management that may occur as part of more formal explanatory studies.

In conclusion, analysis of data from the MESS study indicates that the risk of secondary generalised seizures, in those people who have experienced only partial seizures at the point of diagnosis, have a low risk of subsequent tonic-clonic seizures and that treatment with AEDs with the aim of preventing future such seizures is probably inappropriate. The key factor to be considered in such subjects will be the potential effect of AEDs on the frequency of future partial seizures, though the impact of such a policy may still be limited.

## **Acknowledgements**

This work was supported by a grant from the Medical Research Council (ISRCTN: 98767960).

None of the authors have competing interests. JR and JH have undertaken statistical analysis. DC was principle investigator for the MESS study. AM took the lead in analysis of the original MESS data and in the clinical supervision of this statistical analysis

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## Appendix

### Statistical Model

We assume that each individual experiences seizures according to a Poisson process, with an underlying event rate,  $\lambda_i v_i$ . The term  $\lambda_i$  depends on covariates and  $v_i$  is a random effects term that measures the degree of heterogeneity in the population. Let the explanatory variables be entered into the covariate  $Z_{1i}$ , and  $\lambda_i$  is related to  $Z_{1i}$  using a log-link. It is assumed that treatment acts multiplicatively on the event rate, so that the post-randomisation event rate for those susceptible to post-randomisation seizure recurrence is  $\lambda_i \psi_i v_i$ , where  $\psi_i$  is the seizure rate modifier. The treatment covariate  $Z_{2i}$  contains an intercept term and a treatment indicator, as well as other explanatory variables and interaction terms. A log-link relates  $\psi_i$  to  $Z_{2i}$ .

For each individual, the parameter  $p_i$  denotes the probability that an individual at risk of seizure recurrence during follow-up. The explanatory variables that are important in determining whether an individual is at risk of seizure recurrence are entered into the covariate  $W_i$ , and  $p_i$  is related to  $W_i$  using a logit link.

In summary,

$$\begin{aligned}\lambda_i &= \exp(\beta'_1 z_{1i}) \\ \psi_i &= \exp(\beta'_2 z_{2i}) \\ p_i &= \frac{\exp(\kappa' w_i)}{1 + \exp(\kappa' w_i)}\end{aligned}$$

Where  $\beta_1$ ,  $\beta_2$  and  $\kappa$  are vectors of regression coefficients.

### Regression Coefficients

Table 6 shows the estimated regression coefficients for the two models. The reference group contains individuals with partial seizures pre-randomisation, with a normal EEG and randomised to deferred treatment. Age is age in years at randomisation minus the mean age at randomisation, which was 30 years. The estimated regression coefficients can be used to derive the degree of acceleration or deceleration in the time to first seizure. A  $\beta$  regression coefficient  $> 0$  ( $< 0$ ) would indicate an increased (decreased) seizure rate relative to the seizure rate in the reference group and an ensuing decrease (increase) in the time to next seizure. A  $\kappa$  regression coefficient  $> 0$  ( $< 0$ ) would indicate an increase (decrease) in the at risk proportion relative to the susceptible proportion in the reference group.

Regression Coefficient	Estimates (standard errors) for the following models:	
	Time to First Seizure	Time to First Tonic-Clonic Seizure
$\alpha$	2.044 (0.111)	2.068 (0.113)
$\lambda_i$ Intercept	-4.140 (0.086)	-4.127 (0.085)
Tonic-Clonic only	-1.064 (0.095)	-1.077 (0.095)
2° Tonic-clonic	-0.680 (0.098)	-0.692 (0.097)
Partial only	Reference	Reference
Age	-0.004 (0.001)	-0.004 (0.001)
$\psi_i$ Intercept	-1.276 (0.371)	-2.889 (0.620)
Deferred treatment	Reference	Reference
Immediate treatment	0.494 (0.388)	0.504 (0.681)
Tonic-Clonic only	0.806 (0.389)	2.388 (0.631)
2° Tonic-Clonic	0.717 (0.398)	1.533 (0.644)
Partial only	Reference	Reference
Immediate × T-C	-0.752 (0.399)	-0.799 (0.688)
Immediate × 2° T-C	-0.958 (0.404)	-0.596 (0.705)
Normal EEG	Reference	Reference
Abnormal EEG	0.887 (0.394)	1.537 (0.681)
Immediate × Abnormal	-0.958 (0.248)	-1.110 (0.288)
Abnormal × T-C	-0.863 (0.417)	-1.490 (0.690)
Abnormal × 2° T-C	-0.594 (0.425)	-0.537 (0.705)
Intercept	0.945 (0.426)	-1.654 (0.317)
Tonic-Clonic only	-0.921 (0.441)	1.545 (0.317)
2° Tonic-Clonic	-1.140 (0.450)	1.382 (0.323)
Partial only	Reference	Reference
Normal EEG	Reference	Reference
Abnormal EEG	-0.504 (0.506)	0.465 (0.157)
Abnormal × T-C	1.083 (0.546)	Not Significant
Abnormal × 2° T-C	1.876 (0.576)	Not Significant
-Log-likelihood (d.f.)	7637 (1313)	6851 (1315)

Table 6: Estimated regression coefficients for the joint models.

For each of the joint models the estimated regression coefficients appearing in  $\lambda_i$  correspond to the underlying seizure rates. As would be expected the estimated regression coefficients under each of the joint models are very similar. The low values of  $\alpha$ , for each of the models, shows that there is considerable heterogeneity within the population. To aid understanding of the effect of the explanatory variables on seizures we can use the estimated regression coefficients to obtain estimates of the underlying seizure rates, cure rates and post-randomisation seizure rate modifiers, using the link functions discussed. The expected number of days between seizures pre-randomisation can be calculated by  $1/\lambda_i$  and the expected number of days between seizures post-randomisation can be calculated by  $1/(\lambda_i\psi_i)$ .