APPENDIX O

1 Network meta-analysis of pharmacological interventions in the treatment of epilepsy

1.1 Introduction

The results of conventional meta-analyses of direct evidence alone (as presented in the GRADE profiles in appendix N) make it difficult to determine which intervention is most effective in the treatment of epilepsy. The challenge of interpretation has arisen for two reasons:

- In isolation, each pair-wise comparison does not inform the choice among all the different AEDs, and in addition direct evidence is not available for some pair-wise comparisons in a randomised controlled trial (for example, adjunctive phenytoin versus placebo for an adult population with refractory focal seizures).

- There are frequently multiple overlapping comparisons (for example, adjunctive lamotrigine versus placebo, gabapentin versus placebo and gabapentin versus lamotrigine for an adult population with focal seizures), that could potentially give inconsistent estimates of effect.

To overcome these problems, a hierarchical Bayesian network meta-analysis (NMA) was performed. This type of analysis allows for the synthesis of data from direct and indirect comparisons and allows for the ranking of different interventions. In this case, in order of efficacy, defined as:

- the proportion of people achieving seizure freedom in newly diagnosed focal seizures and
- the proportion of people achieving at least 50% reduction in seizure frequency in refractory focal seizures

and tolerability, defined as

- the proportion of people who withdraw due to adverse events.

The analysis also provided estimates of effect (with 95% credible intervals[1]) for each intervention compared to one another and compared to a single baseline risk. These

[1] Credible intervals are the Bayesian equivalent of confidence intervals and are based on the percentiles of the posterior distribution of the parameter of interest.

estimates provide a useful clinical summary of the results and facilitate the formation of recommendations based on the best available evidence. Furthermore, these estimates were used to parameterise treatment effectiveness of first line interventions in the de novo cost-effectiveness modelling presented in appendix P.

Conventional fixed effects meta-analysis assumes that the relative effect of one treatment compared to another is the same across an entire set of trials. In a random effects model, it is assumed that the relative effects are different in each trial but that they are from a single common distribution and that this distribution is common across all sets of trials.

Network meta-analysis requires an additional assumption over conventional meta-analysis. The additional assumption is that intervention A has the same effect on patients in trials of intervention A compared to intervention B as it does for patients in trials of intervention A versus intervention C, and so on. Thus, in a random effects network meta-analysis, the assumption is that intervention A has the same effect distribution across trials of A versus B, A versus C and so on.

This specific method is usually referred to as mixed-treatment comparisons analysis but we will continue to use the term network meta-analysis to refer generically to this kind of analysis. We do so since the term "network" better describes the data structure, whereas "mixed treatments" could easily be misinterpreted as referring to combinations of treatments.

1.2 Methods

1.2.1 Study selection and data collection

To estimate the odds ratios and relative risks, we performed a NMA that simultaneously used all the relevant randomised controlled trial evidence from the clinical evidence review [1]. As with conventional meta-analyses, this type of analysis does not break the randomisation of the evidence, nor does it make any assumptions about adding the effects of different interventions. The effectiveness of a particular treatment strategy combination will be derived only from randomised controlled trials that had that particular combination in a trial arm.

From the outset, we sought to minimise any clinical or methodological heterogeneity by focusing the analysis on specific patient subgroups, identifying similar outcomes and including only RCTs that followed patients for a minimum and comparable length of time, and which included anti-epileptic drugs (AEDs) whose dosages were within the

therapeutic range as indicated by the BNF and SPC. Based on this principle, we chose to perform a NMA for newly diagnosed and refractory focal seizures for an adult population. The main justification was that the evidence on focal seizures included multiple comparisons and a NMA would allow us to synthesize the evidence in a more comprehensive way. Furthermore, we chose to conduct the analysis on an adult population, mainly because the clinical and cost effectiveness of treating focal seizures in an adult population was one of the priority clinical questions for the guideline and also because the evidence in children was chiefly one study per comparison. Thus, a NMA would not add considerably to the evidence base for children.

As such, four networks of evidence were identified, defined by their type of treatment: either monotherapy or adjunctive treatment, and outcome measure:

- Proportion of people achieving seizure freedom (henceforth referred to as seizure freedom);
- Proportion of people achieving at least 50% reduction in seizure frequency (henceforth referred to as 50% reduction in seizure frequency);
- Proportion of people withdrawing due to adverse events (henceforth referred to as withdrawal due to adverse events).

Network 1: Seizure freedom in monotherapy for newly diagnosed focal seizures

- Evidence for seizure freedom in newly diagnosed focal seizures in an adult population receiving monotherapy

Network 2: Withdrawal due to adverse events in monotherapy for newly diagnosed focal seizures

- Evidence for withdrawal due to adverse events in newly diagnosed focal seizures in an adult population receiving monotherapy

Network 3: 50% reduction in seizure frequency in adjunctive therapy for refractory focal seizures

- Evidence for 50% reduction in seizure frequency in refractory focal seizures in an adult population receiving adjunctive treatment.

Network 4: Withdrawal due to adverse events in adjunctive therapy for refractory focal seizures

- Evidence for withdrawal due to adverse events in refractory focal seizures in an adult population receiving adjunctive treatment.

1.2.2 Outcome measures

The NMA evidence reviews for interventions considered two clinical efficacy outcomes identified from the clinical evidence review; seizure freedom and 50% reduction in seizure frequency and the tolerability outcome, defined by withdrawal due to adverse events. Withdrawal due to lack of efficacy was not included in the list of outcome measures as it was less reported across the studies compared to the other efficacy outcomes (seizure freedom, at least 50% reduction in seizure frequency). Moreover, the GDG considered that seizure freedom for newly diagnosed population and at least 50% reduction in seizure frequency for refractory population were more important clinical outcomes for testing AED efficacy.

The first two outcomes, seizure freedom and 50% reduction in seizure frequency indicate AED efficacy, whereas withdrawal due to adverse event indicates the tolerability to the AED.

Dichotomous outcome measures were chosen mainly for pragmatic reasons. They represented the outcome measures reported in most trials and the outcomes that the GDG had previously established as important outcomes for the evidence reviews. Seizure freedom for newly diagnosed focal seizures and 50% reduction in seizure frequency were reasonable and common measures of efficacy and were more useful than continuous outcome measures, such as time to first seizure or time to exit/withdrawal of allocated treatment. Dichotomous outcomes also allow for easier interpretation. Outcome measures were calculated on an intention-to-treat basis (i.e. the analysis was based on the total number of randomly assigned participants), regardless of how the original study investigators analysed their data. Approaching the data conservatively, we assumed that missing participants did not respond to treatment.

1.2.3 Comparability of interventions

The interventions compared in the model were those found in the randomised controlled trials included in the clinical evidence review already presented in chapter

10 of the full guideline and in appendix N. If an intervention was evaluated in a study that met the inclusion criteria for the network (that is if it reported at least one of the outcomes of interest and matched the inclusion criteria for the meta-analysis) then it was included in the network meta-analysis, otherwise it was excluded.

The AEDs included in the first two networks on monotherapy for newly diagnosed focal seizures were:

- carbamazepine (CBZ)
- lamotrigine (LTG)
- oxcarbazepine (OXC)
- gabapentin (GBP)
- topiramate (TPM)
- vigabatrin (VGB)
- sodium valproate (VPA)
- phenytoin (PHT)
- clonazepam (CLN) was included only in the second network (withdrawal due to adverse events in monotherapy for a newly diagnosed adult population).

The pharmacological interventions included in both the third and fourth networks on adjunctive treatment for refractory focal seizures were:

- lamotrigine (LTG)
- vigabatrin (VGB)
- gabapentin (GBP)
- levetiracetam (LEV)
- topiramate (TPM)
- oxcarbazepine (OXC)
- pregabalin (PRE)
- lacosamide (LCS)
- eslicarbazepine (ESL)
- zonisamide (ZNM)
- sodium valproate (VPA)
- levetiracetam extended release (LEV-XR)
- lamotrigine extended release (LTG-XR)

- tiagabine (TGB)
- carbamazepine (CBZ) and phenytoin (PHT) only in the third network (50% reduction in seizure frequency in adjunctive therapy for a refractory adult population)
- and clobazam (CLB) and felbamate (FBM) only in the fourth network (withdrawal due to adverse events in adjunctive therapy for a refractory adult population)

The details of these interventions can be found in the clinical evidence review in chapter 10 of the full guideline and appendix N.

1.2.4 Baseline risk

The baseline risk is defined here as the adult or young person's risk of achieving the outcome of interest (seizure freedom, 50% reduction in seizure frequency, withdrawal due to adverse events) in the "control" group. This figure is useful because it allows us to convert the results of the NMA from odds ratios to relative risks.

Deriving the figures from our randomised controlled trials involved two different routes:

- Monotherapy for newly diagnosed focal seizures: by aggregating the number of people achieving seizure freedom or withdrawing due to adverse events across the carbamazepine arms of the studies included in the monotherapy networks and dividing by the aggregate sample size from the same arms. Thus, carbamazepine was assigned the position of baseline drug (control group), as carbamazepine is the standard AED for monotherapy in newly diagnosed focal seizures.

- Adjunctive treatment in refractory focal seizures: by aggregating the number of people achieving at least 50% reduction in seizure frequency and withdrawing due to adverse events across the placebo arms included in the adjunctive treatment networks and dividing by the aggregate sample size from the same arms.

This method produced a baseline probability of 36.3% for seizure freedom and 24.2% for withdrawal due to adverse events for monotherapy in newly diagnosed population and 15% for 50% reduction in seizure frequency and 4.1% for withdrawal due to adverse events for adjunctive therapy in refractory population.

1.2.5 Statistical analysis

A hierarchical Bayesian network meta-analysis (NMA) was performed using the software WinBUGS [2]. We adapted a multi-arm random effects model template for the monotherapy networks and a three-arm random effects model template for the adjunctive treatment networks, both from the University of Bristol website (https://www.bris.ac.uk/cobm/research/mpes/mtc.html). This model accounts for the correlation between arms in trials with any number of trial arms.

In order to be included in the analysis, a fundamental requirement is that each treatment is connected directly or indirectly to every other intervention in the network. For each population and outcome subgroup, a diagram of the evidence network was produced in figures 1a-1b and presented in section 1.3.

The model used was a random effects logistic regression model, with parameters estimated by Markov chain Monte Carlo simulation. As it was a Bayesian analysis, for each parameter the evidence distribution is weighted by a distribution of prior beliefs. A non-informative prior distribution was used to maximise the weighting given to the data. These priors were normally distributed with a mean of 0 and standard deviation of 10,000.

For the three first analyses, a series of 100,000 burn-in simulations were run to allow convergence and then a further 20,000 simulations were run to produce the outputs. For the fourth network, 80,000 burn-in simulations were run to allow convergence and then a further 40,000 simulations were run to produce the outputs. Convergence was assessed by examining the history and kernel density plots.

We tested the goodness of fit of the model by calculating the residual deviance. If the residual deviance is close to the number of unconstrained data points (the number of trial arms in the analysis) then the model is explaining the data well.

The results, in terms of relative risk, of pair-wise meta-analyses are presented in the clinical evidence review (Appendix N). In preparation for the NMA, these conventional meta-analyses were re-run to produce odds ratios and these are presented as part of the NMA results section.

The outputs of the NMA were odds ratios. Odds ratios and their 95% credible intervals were generated for every possible pair of comparisons by combining direct and indirect evidence in the network. To be consistent with the comparative

effectiveness results presented elsewhere in the clinical evidence review and for ease of interpretation, relative risks were computed from the outputs of the NMA. Relative risks were derived from the odds ratios for each intervention compared back to a "control" group, using the baseline risk as described above and the following formula:

$$RR = \frac{OR}{(1 - P_0) + (P_0 \times OR)}$$

where P_o is the baseline risk.

We estimated the RR for each of the 20,000 simulations, treating P_o as a constant. The point estimate of the RR was taken to be the median of the 20,000 simulations and the 95% confidence intervals for the RR were taken to be the 2.5th and 97.5th centiles from the distribution of the RR.

We also assessed the probability that each intervention was the best treatment by calculating the relative risk of each intervention compared to control group and counting the proportion of simulations of the Markov chain in which each intervention had the highest relative risk. Using this same method, we also calculated the overall ranking of interventions according to their relative risk compared to control group.

A key assumption behind NMA is that the network is consistent. In other words, it is assumed that the direct and indirect treatment effect estimates do not disagree with one another. Discrepancies between direct and indirect estimates of effect may result from several possible causes. First, there is *chance* and if this is the case then the network meta-analysis results are likely to be more precise as they pool together more data than conventional meta-analysis estimates alone. Second, there could be differences between the trials included in terms of their clinical or methodological characteristics. Differences that could lead to inconsistency include:

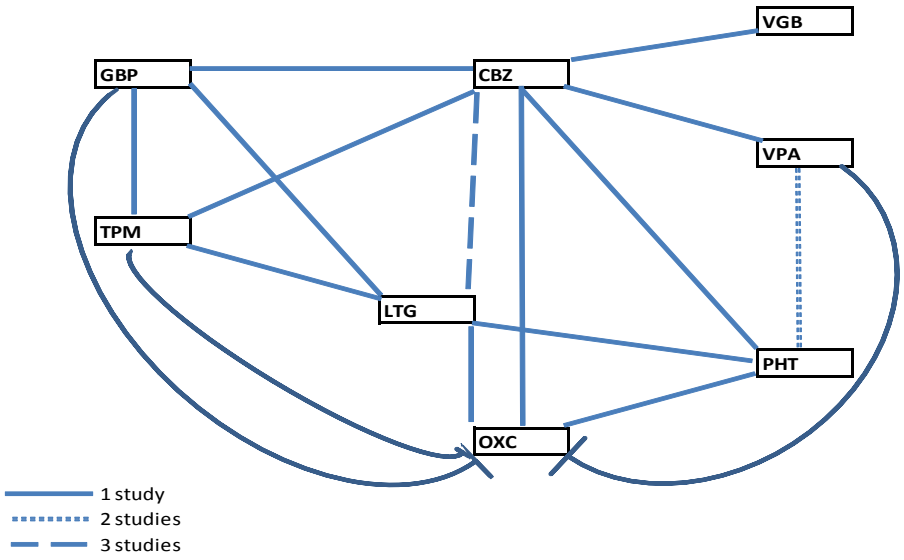
- Different populations (e.g. gender, age)
- Different interventions (doses)
- Different follow-up periods (1 year, 2 years)

This heterogeneity is a problem for network meta-analysis but may be dealt with by subgroup analysis, meta-regression or by carefully defining inclusion criteria. Inconsistency, caused by heterogeneity, was assessed subjectively by comparing the

odds ratios from the direct evidence (from pair-wise meta-analysis) to the odds ratios from the combined direct and indirect evidence (from NMA). We assumed the evidence to be inconsistent where the odds ratio from the NMA did not fit within the confidence interval of the odds ratio from the direct comparison. Where inconsistency between observed treatment effects was identified, we sought to find the heterogeneity by examining the details of the study design, population, interventions and outcomes of the relevant trials.

1.3 *Results*

A total of 86 studies from the original evidence review met the inclusion criteria for at least one network. Figures 1a-1d show the 4 networks created by eligible comparisons for each NMA.



Figures 1a: Network 1: Monotherapy in newly diagnosed focal seizures- seizure freedom

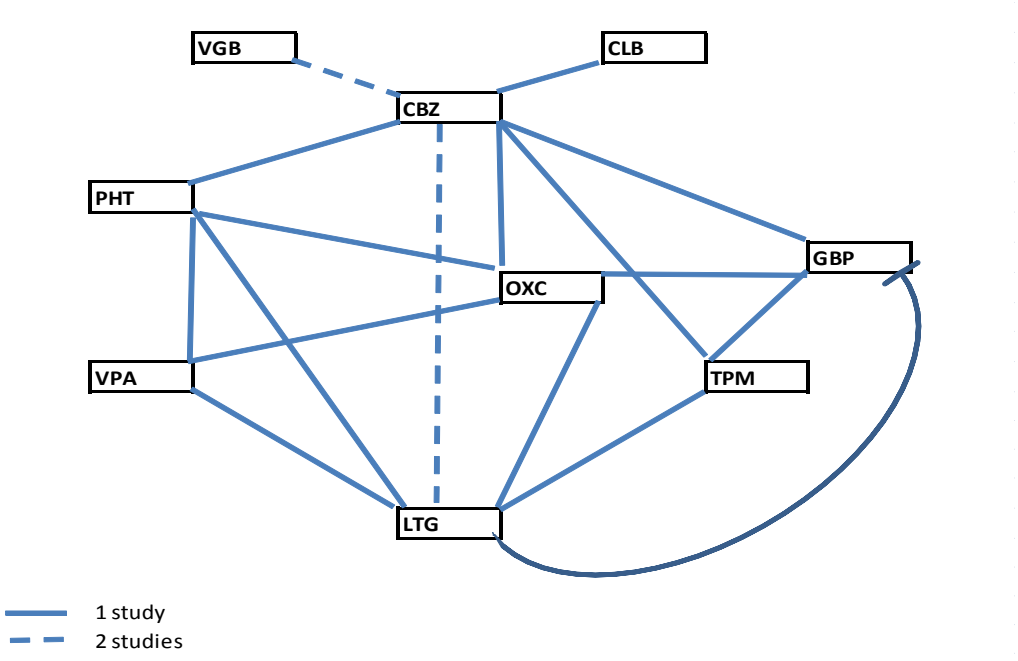


Figure 1b: Network 2: Monotherapy in newly diagnosed focal seizures- withdrawal due to adverse events.

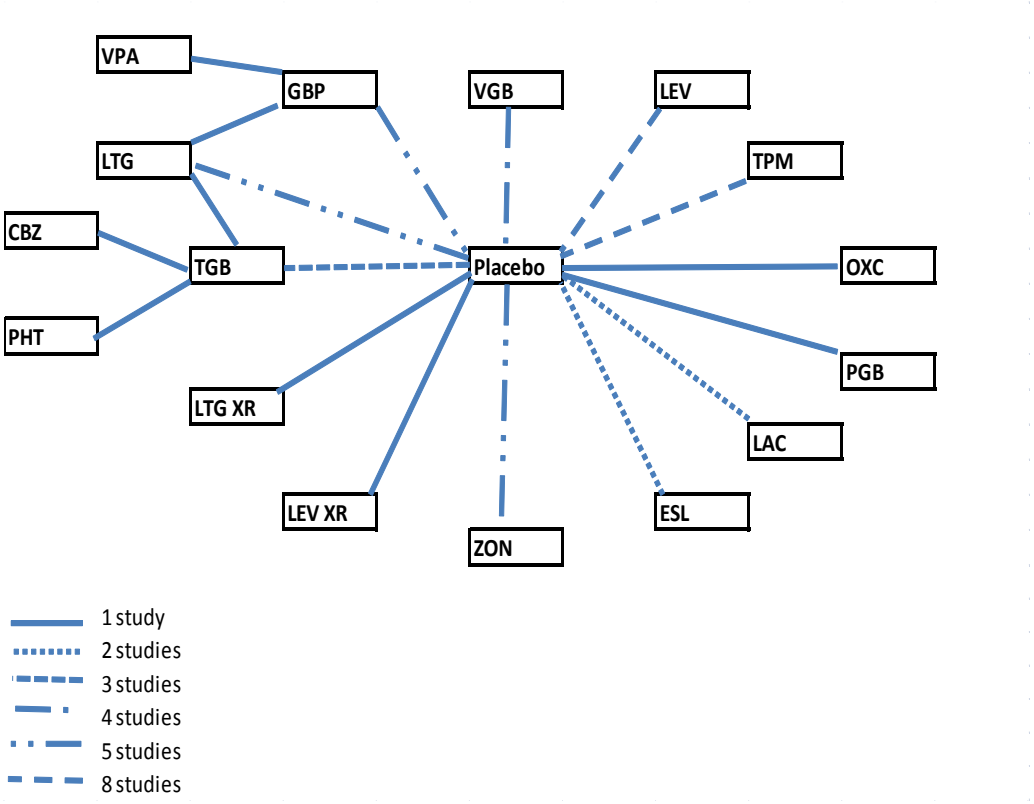


Figure 1c: Network 3: Adjunctive therapy in refractory focal seizures- 50% reduction in seizures.

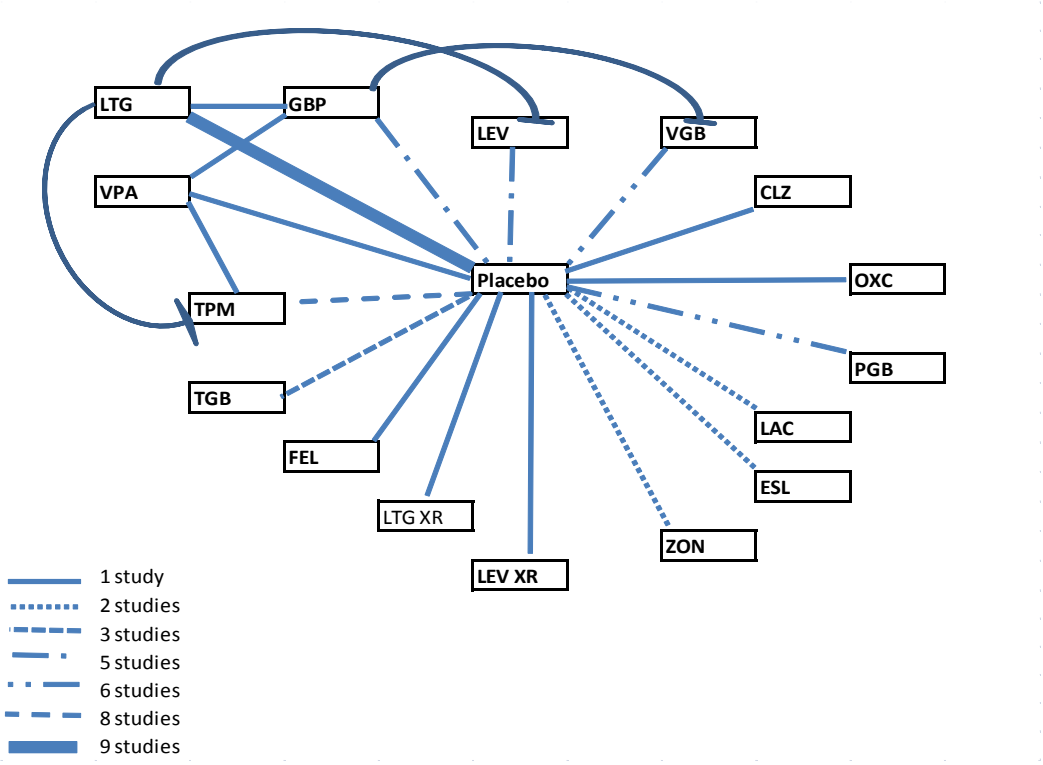


Figure 1d: Network 4: Adjunctive therapy in refractory focal seizures- Withdrawal due to adverse events.

The trial data from the nine studies in people with newly diagnosed focal seizures who achieved seizure freedom on monotherapy are shown in Table 1. The trial data from the 12 studies of people with newly diagnosed focal seizures who withdrew (monotherapy) due to adverse events are presented in Table 2. The trial data from the 53 studies of people with refractory focal seizures who achieved 50% reduction in seizure frequency are presented in Table 3. Data relating the proportion of patients with refractory focal seizures who withdrew (adjunctive) due to adverse events is included in Table 4.

Table 1: Trial data for seizure freedom (monotherapy for newly diagnosed focal seizures)

			Active treatment		Comparator	
Active Treatment	**Comparator**	**Study**	**N**	**NR**	**N**	**NR**
LTG	CBZ	Marson 2007 [3]	356	103	347	125
OXC	CBZ		189	66		
GBP	CBZ		337	81		
TPM	CBZ		338	112		
LTG	CBZ	Brodie 1995 [4]	73	16	73	23
VGB	CBZ	Tanganelli 1996 [5]	26	12	25	14
VPA	CBZ	Callaghan 1985 [6]	27	12	31	11
PHT	CBZ		21	12		
LTG	PHT	Steiner 1999 [7]	44	9	46	11
OXC	VPA	Christe 1997 [8]	76	29	78	33
OXC	PHT	Bill 1997 [9]	84	39	98	55
VPA	PHT	Turnbull 1985 [10]	33	9	31	9
VPA	PHT	Rastogi 1991 [11]	14	6	13	2

N; number of participants, NR; number of responders

Nine studies were included for seizure freedom on monotherapy for newly diagnosed focal seizures (table 1). The mean age of participants in these trials was 29.7 years (range 8- 91) with some studies also including elderly participants (Bill, 1997, Callaghan, 1985, Brodie, 1995 and Steiner, 1999). The minimum age of participants in all studies was 12 years with the exception of Rastogi (1991) and Callaghan (1985) that included children aged 8 years and older.

The duration of the treatment was comparable across the nine trials included for this analysis; Brodie (1995), Steiner (1999), Christe (1997), Bill (1991) and Callaghan (1985) had set up a treatment period of 48 weeks, whereas Rastogi (1991) and Tanganelli (1996) followed participants for 8 and 4-24 weeks of treatment respectively. The longest study was conducted by Turnbull (1985) which lasted 2 years.

The majority of AEDs used in these nine studies were consistently in accordance with the usual therapeutic dosages as recommended by the British National Formulary (BNF). However, sodium valproate in some studies was prescribed in lower doses than its usual therapeutic range; in Turnbull and Callaghan (600mg/daily) and in Rastogi (15mg/kg/day) (BNF recommended is 1-2 gr/day or 20-30 mg/kg/daily). The highest amount of phenytoin also given in Bill's trial was 800 mg/day whereas the highest BNF recommended threshold is 500 mg/daily. Finally, carbamazepine in both studies by Callaghan (1985) and Brodie (1997) were prescribed in lower doses than the ones recommended by BNF; carbamazepine was given in a dose of 600 mg/daily whereas the usual dosage is 0.8-1.2gr/day).

Table 2: Trial data of withdrawal due to adverse events (monotherapy for newly diagnosed focal seizures)

			Active treatment		**Comparator**	
Active Treatment	**Comparator**	**Study**	**N**	**NW**	**N**	**NW**
LTG	CBZ	Marson 2007 [3]	370	60	368	96
OXC	CBZ		202	46		
GBP	CBZ		366	62		
TPM	CBZ		366	95		
LTG	CBZ	Brodie 1995 [4]	131	17	129	35
GBP	CBZ	Chadwick 1998 [12]	146	13	74	18

VGB	CBZ	Chadwick 1999 [13]	229	43	230	61
VGB	CBZ	Tanganelli 1996 [5]	29	0	39	1
CLN	CBZ	Mikkelsen 1981 [14]	17	7	19	4
PHT	CBZ	Ramsay 1983 [15]	42	8	45	8
LTG	VPA	Fakhoury 2004 [16]	105	14	53	11
LTG	PHT	Steiner 1999 [7]	86	13	95	18
OXC	VPA	Christe 1997 [8]	128	15	121	10
OXC	PHT	Bill 1997 [9]	143	5	144	16
VPA	PHT	Turnbull 1985 [10]	33	9	31	11

1 N; number of participants, NW; number of participants withdrawing

Twelve studies were included for the NMA of withdrawal due to adverse events on monotherapy for newly diagnosed focal seizures (Table 2). The mean age of participants in these trials was 33.1 years (range 6- 91), with all studies including also elderly participants except Turnbull (1985) and Christe (1997) that included participants up to the age of 65 years. The minimum age of participants in all studies was 12 years with the exception of Mikkelson (1981) that included children aged 6 years and older.

The duration of the treatment varied across the 12 trials included for this analysis ; Brodie (1995), Steiner (1999), Christe (1997), Bill (1991), Mikkelson (1981) and Chadwick (1999) had set up a treatment period of 1 year (48-52 weeks), whereas Fakhoury (2004), Tanganelli (1996) and Chadwick (1998) followed participants for 8, 16 and 24 weeks of treatment respectively. The longest studies were conducted by Ramsay (1983) and Turnbull (1985) which lasted up to 2 years.

The majority of drugs used in these 12 studies were consistently in accordance with the usual therapeutic dosages as recommended by the BNF. However, sodium valproate in Turnbull was prescribed in lower doses (600mg/daily) than its usual therapeutic range (BNF recommended is 1-2 gr/day or 20-30 mg/kg/daily); carbamazepine also in both studies by Chadwick (1998, 1999)) and Brodie (1995) were prescribed in lower doses than the ones recommended by BNF; carbamazepine was given in a dose of 600 mg/daily whereas the usual dosage is 0.8-1.2gr/day.The highest amount of phenytoin also given in Bill's trial was 800 mg/day whereas the highest BNF recommended threshold is 500 mg/daily. Finally, the maximum dosage of vigabatrin given in Chadwick (1999) was 4 gr/daily although the maximum recommended by the BNF is 3gr in daily basis.

Table 3: Trial data of 50% reduction in seizure frequency (adjunctive treatment for refractory focal seizures)

			Active treatment		**Comparator**	
Active Treatment	**Comparator**	**Study**	**N**	**NR**	**N**	**NR**
LTG	Placebo	**Matsuo 1993** [17]	143	33	73	12
LTG XR	Placebo	**Naritoku 2007** [18]	121	49	122	29
LTG	TGB	**Chmielewska 2001** [19]	22	11	26	11
LEV XR	Placebo	**Peltola 2009** [20]	79	34	79	23
LEV	Placebo	**Zhou 2008** [21]	14	8	14	2

LEV	Placebo	**Xiao 2009** [22]	28	13	28	11
LEV	Placebo	**Tsai 2006** [23]	47	20	47	5
LEV	Placebo	**Ben-Menachem 2000** [24]	181	72	105	17
LEV	Placebo	**Cereghino 2000** [25]	199	76	95	7
LEV	Placebo	**Wu 2009** [26]	103	57	103	26
LEV	Placebo	**Shorvon 2000** [27]	212	53	112	11
TPM	Placebo	**Korean Topiramate Group 1999** [28]	91	45	86	11
TPM	Placebo	**Yen 2000** [29]	23	11	23	3
TPM	Placebo	**Guberman 2002** [30]	171	75	92	22
TPM	Placebo	**Sharief 1996** [31]	23	8	24	2
TPM	Placebo	**Tassinari 1996** [32]	30	14	30	3
TPM	Placebo	**Ben-Menachem 1996** [33]	28	12	28	0
TPM	Placebo	**Faught 1996** [34]	136	54	45	8
TPM	Placebo	**Privitera 1996** [35]	96	40	47	4
GBP	Placebo	**Yamauchi 2006** [36]	127	20	82	5
GBP	Placebo	**US Gabapentin group 1993** [37]	155	30	98	8
GBP	Placebo	**UK Gabapentin group 1990** [38]	61	14	66	6
GBP	Placebo	**Sivenius 1991** [39]	27	5	18	3
GBP	Placebo	**Anhut 1994** [40]	163	36	109	10
GBP	LTG	**Sethi 2002** [41]	27	21	25	23
GBP	VGB	**Lindberger 2000** [42]	50	27	52	34
			Active treatment		**Comparator**	
Active Treatment	**Comparator**	**Study**	**N**	**NR**	**N**	**NR**
GBP	VPA	**Maton 1998**[43]	10	2	15	6
TGB	Placebo	**Uthman 1998** [44]	145	33	91	4
TGB	Placebo	**Sachdeo 1997** [45]	211	54	107	9
TGB	Placebo	**Kalviainen 1998** [46]	77	11	77	5
VGB	Placebo	**Dean 1999** [47]	43	22	45	3
VGB	Placebo	**French 1996** [48]	93	40	90	17
VGB	Placebo	**Grunewald 1994** [49]	22	9	23	4

PRE	Placebo	**French 2003** [50]	267	108	100	14
PRE	Placebo	**Elger 2005** [51]	268	103	73	8
PRE	Placebo	**Lee 2009** [52]	119	55	59	19
PRE	Placebo	**Arroyo 2004** [53]	191	54	97	6
PRE	Placebo	**Beydoun 2005** [54]	215	98	98	9
LZM	Placebo	**Halasz 2009** [55]	322	120	163	41
LZM	Placebo	**Ben Menachem 2007** [56]	215	79	97	21
ZNM	Placebo	**Brodie 2005** [57]	174	74	120	21
ZNM	Placebo	**Sackellares 2004** [58]	78	21	74	12
ZNM	Placebo	**Schmidt 1993** [59]	71	20	68	6
ZNM	Placebo	**Faught 2001** [60]	118	41	85	16
ESC	Placebo	**Elger 2009** [61]	300	93	102	15
ESC	Placebo	**Elger 2007** [62]	97	46	47	13
OXC	Placebo	**Barcs 2000** [63]	521	205	173	22
TGB	PHT	**Cramer 2001** [64]	105	23	101	28
TGB	CBZ	**Cramer 2001** [64]	67	14	76	33
LTG	Placebo	**Loiseau 1990** [65]	23	7	Cross over study	
LTG	Placebo	**Schapel 1993** [66]	41	9	Cross over study	
LTG	Placebo	**Binnie 1989** [67]	34	2	Cross over study	

N; number of participants, NR; number of responders

Fifty –five studies were included for the NMA for 50% reduction in seizure frequency in adjunctive therapy in refractory focal seizures (Table 3). The mean age (of participants in all trials was 33.9 years (range 12-77). The minimum age of participants in all studies was 16 years with the exception of Sethi (2002), Lindberger (2000), Uthman (1998), Sachdeo (1997), Tassinari (1996), Faught (1996), Brodie (2005), Naritoku (2007), Anhut (1994) and Peltola (2009) that included children aged 10-12 years and older.

The duration of treatment for the majority of studies in this network was 20 weeks. However, Cereghino (2000), Zhou (2008), Matsuo (1993), Lindberger (2000) and two cross over studies (Loiseau (1990) and Schapel (1993)) had set up a treatment period up to 32 weeks. The longest study was conducted by Cereghino (2000) which lasted 38 weeks.

The majority of drugs used in these 55 studies were consistently in accordance with the usual therapeutic dosages as recommended by the BNF. However, the highest amount of topiramate given in Privitera's trial was 1000 mg/day whereas the highest BNF recommended threshold is 800 mg/daily. One of the zonisamide's doses in Brodie (2005) trial (100mg/daily) was lowest than the recommended range of dosage by the BNF (300-500 mg/daily), whereas tiagabine in Uthman study was given in higher dose (56 mg/daily) than the maximum recommended (45 mg/daily). Lastly, vigabatrin was given in some studies (Lindberger and Dean) in higher doses, 4 and 6 gr/daily respectively, than the maximum recommended by the BNF for this drug (3gr/daily).

Table 4: Trial data of withdrawal due to adverse events (adjunctive treatment for focal seizures)

			Active treatment		**Comparator**	
Active Treatment	**Comparator**	**Study**	**N**	**NR**	**N**	**NR**
LTG	Placebo	**Matsuo 1993** [17]	143	13	73	1
GBP	Placebo		211	54		
LTG	Placebo	**Matsuo 1996** [68]	8	1	4	0
CLO	Placebo	**Koeppen 1987** [69]	129	3	129	0
LTG XR	Placebo	**Naritoku 2007** [18]	121	12	122	2
LEV XR	Placebo	**Peltola 2009** [20]	79	5	79	2
FEL	Placebo	**Bourgeois 1993** [70]	30	2	34	0
TPM	Placebo	**Maedor 2003** [71]	34	6	13	1
VPA	Placebo		29	2		
LEV	Placebo	**Tsai 2006** [23]	47	1	47	3
TPM	Placebo	**Ben-Menachem 1996** [33]	28	6	28	0
LEV	Placebo	**Cereghino 2000** [25]	199	13	95	5
LEV	Placebo	**Wu 2009** [26]	103	0	103	2
LEV	Placebo	**Shorvon 2000** [27]	212	23	112	6
TPM	Placebo	**Korean Topiramate Group 1999** [28]	91	7	86	3
TPM	Placebo	**Guberman 2002** [30]	171	13	92	2
TPM	Placebo	**Sharief 1996** [31]	23	6	24	1
TPM	Placebo	**Tassinari 1996** [32]	30	4	30	1

TPM	Placebo	**Faught 1996** [34]	136	12	45	3
TPM	Placebo	**Privitera 1996** [35]	96	15	47	1
TPM	Placebo	**Yen 2000** [29]	23	2	23	2
GAB	Placebo	**US Gabapentin group 1993** [37]	155	4	98	1
GAB	Placebo	**UK Gabapentin group 1990** [38]	61	7	66	4
GAB	Placebo	**Yamuauchi 1993** [36]	127	7	82	1
GAB	Placebo	**Anhut 1994** [40]	163	11	109	4
GBP	VGB	**Lindberger 2000** [42]	50	7	52	7
			Active treatment		**Comparator**	
Active Treatment	**Comparator**	**Study**	**N**	**NW**	**N**	**NW**
TPM	VPA	**Aldenkamp 2000** [72]	29	6	30	2
GBP	VPA	**Maton 1998** [43]	10	5	15	2
TPM	LTG	**Blum 2006** [73]	96	24	96	20
LTG	LEV	**Labiner 2009** [74]	132	14	136	24
TGP	Placebo	**Uthman 1998** [44]	145	22	91	7
TGP	Placebo	**Sachdeo 1997** [45]	211	24	107	7
TGP	Placebo	**Kalviainen 1998** [46]	77	17	77	2
VGB	Placebo	**Dean 1999** [47]	43	5	45	1
VGB	Placebo	**French 1996** [48]	93	7	90	2
PRE	Placebo	**French 2003** [50]	267	35	100	5
VGB	Placebo	**Loiseau 1990** [65]	23	2	23	0
VGB	Placebo	**Tartara 1986** [75]	23	1	23	0
VGB	Placebo	**McKee 1993** [76]	24	1	24	0
VGB	Placebo	**Tassinari 1997** [77]	31	1	31	0
PRE	Placebo	**Lee 2009** [52]	119	7	59	0
PRE	Placebo	**Arroyo 2004** [53]	191	27	97	6
PRE	Placebo	**Beydoun 2005** [54]	215	48	98	7
LZM	Placebo	**Halasz 2009** [55]	322	34	163	8
LEV	Placebo	**Ben-Menachem 2000** [24]	181	17	105	9
ZNM	Placebo	**Brodie 2005** [57]	174	36	120	8
ZNM	Placebo	**Sackellares 2004** [58]	78	12	74	1

PRE	Placebo	**Elger 2005** [51]	268	61	73	5
ESC	Placebo	**Elger 2009** [61]	300	32	102	4
ESC	Placebo	**Elger 2007** [62]	97	7	47	4
OXC	Placebo	**Barcs 2000** [63]	521	200	173	15
LTG	Placebo	**Messenheimer 1994** [78]	98	4	98	1
LTG	Placebo	**Sander 1990** [79]	20	1	19	1
			Active treatment		**Comparator**	
Active Treatment	**Comparator**	**Study**	**N**	**NW**	**N**	**NW**
LTG	Placebo	**Jawad 1989** [80]	24	1	24	0
LTG	Placebo	**Schacter 1995** [81]	334	28	112	9
LTG	Placebo	**Storalek 1994** [82]	22	0	**22**	**1**
LTG	Placebo	**Binnie 1989** [67]	34	0	Cross over study	

1 N; number of participants, NW; number of participants withdrawing

Fifty-six studies were included for the NMA of adjunctive therapy for withdrawal due to adverse events in refractory focal seizures (Table 4). The mean age of participants in all trials were 32.6 years (range 12-77).The minimum age of participants in all studies was 16 years with the exception of Lindberger (2000), Uthman (1998), Sachdeo (1997), French (2003), Brodie (2005), Naritoku (2007), Anhut (1994) and Peltola (2009) that included children aged 10-12 years and older.

The duration of treatment for the majority of studies in this network was 12-18 weeks. However, Uthman's study lasted 20 weeks, Kalviainen's trial 22 weeks and, Brodie , Barcs, Matsuo, and Lindberger 's trials had set up a treatment period of 24 weeks. The longest study was conducted by Cereghino (2000) which lasted 38 weeks.

The majority of drugs used in these 56 studies were given consistently with the usual therapeutic dosages as recommended by the BNF. However, the highest amount of topiramate given in Privitera's trial was 1000 mg/day whereas the highest BNF recommended threshold is 800 mg/daily. One of the zonisamide's doses in Brodie (2005) trial (100mg/daily) was lowest than the recommended range of dosage by the BNF (300-500 mg/daily), whereas tiagabine in Uthman study was given in higher dose (56 mg/daily) than the maximum recommended (45 mg/daily). Lastly, vigabatrin was given in some studies (Lindberger and Dean) in higher doses, 4 and 6 gr/daily respectively, than the maximum recommended by the BNF for this drug (3gr/daily).

The clinical evidence reviews considered the quality of the outcome measures according to the modified GRADE evidence profiles. The clinical evidence reviews showed the methodological quality of the outcome measures included in the NMA was moderate to very low.

Network 1: Seizure freedom in monotherapy for newly diagnosed focal seizures

Table 5 summarises the results of the conventional meta-analyses in terms of odds ratios generated from studies directly comparing different interventions. Table 5 also presents the results of the NMA in terms of odds ratios for every possible treatment comparison.

Table 5: Effectiveness (seizure freedom) of interventions in newly diagnosed population focal seizures, results of conventional and network meta-analyses

	0.70 (0.53-0.94)	0.96 (0.63-1.45)	**0.56 (0.32-0.78)**	0.88 (0.64-1.20)	0.67 (0.22, 2.03)	1.44 (0.51-4.16)	2.43 (0.78-7.69)
0.73 (0.43-1.31)							1.22 (0.45-3.33)
0.96 (0.53-1.86)	1.32 (0.70-2.54)					1.19 (0.63-2.27)	1.47 (0.82-2.63)
0.56 (0.27-1.19)	0.77 (0.37-1.59)	0.58 (0.27-1.22)					
0.89 (0.44-1.85)	1.22 (0.58-2.46)	0.93 (0.43-1.89)	1.59 (0.72-3.45)				
0.74 (0.19-2.58)	1.01 (0.21-3.78)	0.78 (0.16-2.95)	1.32 (0.26-5.44)	0.84 (0.17-3.39)			
1.29 (0.62-2.97)	1.75 (0.82-4.05)	1.34 (0.69-2.67)	2.29 (0.93-6.05)	1.45 (0.61-3.80)	1.75 (0.42-8.88)		0.99 (0.49, 2.00)
1.27 (0.63-2.67)	1.75 (0.85-3.56)	1.33 (0.71-2.48)	2.29 (0.98-5.54)	1.44 (0.63-3.43)	1.71 (0.43-8.56)	0.98 (0.49-1.92)	

Results in white are the odds ratios and 95% confidence intervals from the conventional meta-analyses of direct comparisons between the column-defining treatment and the row-defining treatment. Odds ratios greater than 1 favour the column-defining treatment.

Results in gray are the median odds ratios and credible intervals from the NMA of direct and indirect comparisons between the row-defining treatment and the column-defining treatment. Odds ratios greater than 1 favour the row-defining treatment.

Numbers in bold highlight statistically significant results (P<0.05).

Based on the direct comparisons (in white in Table 5), efficacy as assessed by seizure freedom in newly diagnosed focal seizures favours carbamazepine over lamotrigine and gabapentin. No other treatment effects reached statistical significance. The random effects model used for the NMA fit well, with a residual deviance of 21.23 reported. This corresponds well to the total number of trial arms, 22.

Based on the results of the NMA (in grey in Table 5), no AED treatment was found to be significantly more effective than the other. No inconsistency was identified between the direct and NMA results for any comparison. All the median odds ratios of AEDs compared to carbamazepine from the NMA lie within the 95% confidence interval from the direct comparison of the same AEDs.

Table 6 presents the relative risk of each intervention compared to carbamazepine. It also gives the probability that each intervention is most effective. Based on point estimates, distribution of rank and proportion of simulations in which they are the most effective AEDs, valproate and phenytoin were the most effective AEDs in achieving seizure freedom with a probability of 38.5% and 33.9% respectively.

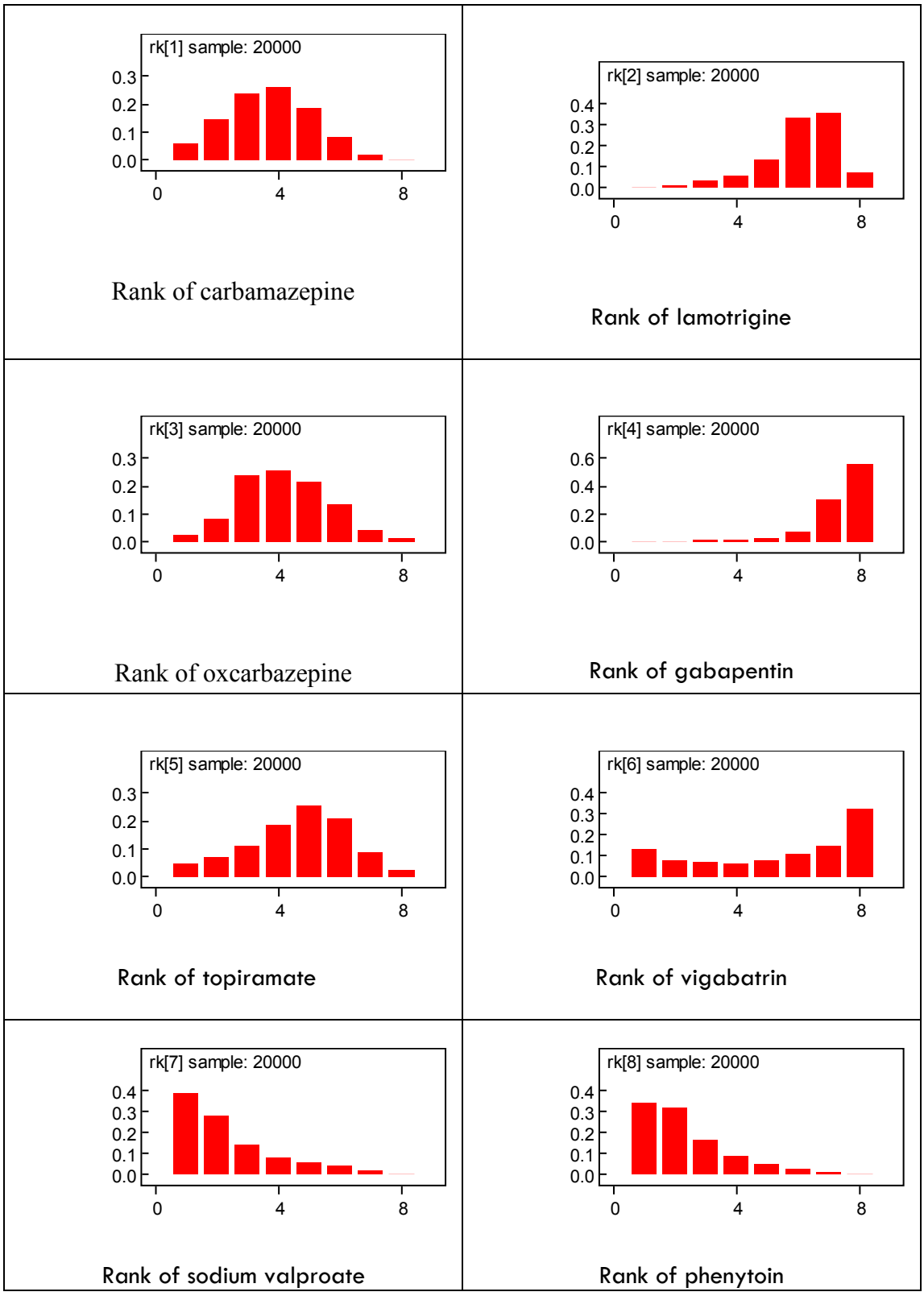
Table 6: Effectiveness of interventions in network 1 compared to carbamazepine

AED*	**^Median relative risk (95% Credible Interval)**	**Probability intervention is most effective (%)**
Carbamazepine	-	5.9%
Lamotrigine	0.81 (0.54, 1.18)	0.5%
Oxcarbazepine	0.97 (0.64, 1.42)	2.3%
Gabapentin	0.67 (0.37, 1.11)	0.5%
Topiramate	0.93 (0.56, 1.41)	4.9%
Vigabatrin	0.82 (0.26, 1.64)	13.2%
Valproate	1.17 (0.72, 1.73)	38.5%
Phenytoin	1.16 (0.73, 1.66)	33.9%

^ Median RR<1, Carbamazepine was more effective compared to the AED
SANAD data dichotomized from time to 12 month remission (year 1) to seizure freedom.

Figure 3 shows the distribution of probabilities of each intervention being ranked at each of 8 positions.

Figure 3: Ranking of interventions in network 1



Ranking is based on the relative risk compared to no treatment and indicates the probability of being the best treatment, second best, third best and so on among the 12 different interventions being evaluated.

Network 2: Withdrawal due to adverse events in monotherapy for newly diagnosed focal seizures

Table 7 summarises the results of the conventional meta-analyses in terms of odds ratios generated from studies directly comparing different interventions. Table 7 also presents the results of the NMA in terms of odds ratios for every possible treatment comparison.

Table 7: Tolerability (withdrawal due to adverse events) of interventions in a newly diagnosed population with focal seizures, results of conventional and network meta-analyses

	0.50 (0.37, 0.69)	0.96 (0.62, 1.44)	**0.52 (0.37-0.78)**	0.99 (0.71- 1.38)	**0.64 (0.41-0.98)**	2.63 (0.61, 11.37)		0.92 (0.31-2.70)
0.48 (0.24-0.89)							1.69 (0.71-4.0)	1.32 (0.59-2.86)
0.68 (0.29-1.34)	1.41 (0.64-2.78)						0.68 (0.29-1.59)	**3.45 (1.23-10.0)**
0.46 (0.21-0.87)	0.96 (0.40-2.00)	0.68 (0.28-1.62)						
0.87 (0.34-1.91)	1.80 (0.72-4.37)	1.28 (0.52-3.46)	1.90 (0.78-4.88)					
0.62 (0.21-1.4)	1.28 (0.38-3.92)	0.91 (0.26-3.10)	1.33 (0.39-4.50)	0.70 (0.18-2.51)				
2.85 (0.51-16.71)	6.01 (0.97-40.38)	4.30 (0.66-30.85)	**6.36 (1.00-44.78)**	3.30 (0.50-24.53)	4.73 (0.71 -38.69)			
0.61 (0.23-1.53)	1.29 (0.55-2.97)	0.92 (0.40-2.29)	1.36 (0.49-3.96)	0.71 (0.25-2.21)	1.02 (0.27-4.00)	0. 21 (0.03-1.55)		1.47 (0.51, 4.16)
1.03 (0.44 - 2.30)	**2.16 (1.00- 4.60)**	1.53 (0.71-3.64)	2.26 (0.90- 6.14)	1.19 (0.42 -3.50)	1.66 (0.49- 6.45)	0.36 (0.05 - 2.37)	1.66 (0.70 - 4.12)	

- Results in white are the odds ratios and 95% confidence intervals from the conventional meta-analyses of direct comparisons between the column-defining treatment and the row-defining treatment. Odds ratios greater than 1 favour the row-defining treatment.
- Results in gray are the median odds ratios and credible intervals from the NMA of direct and indirect comparisons between the row-defining treatment and the column-defining treatment. Odds ratios greater than 1 favour the column-defining treatment.
- Numbers in bold highlight statistically significant results (P<0.05).

Based on the direct comparisons (in white in table 7), tolerability as assessed by withdrawal due to adverse events favours vigabatrin over carbamazepine, gabapentin over carbamazepine and oxcarbazepine over phenytoin. No other treatment effects reached statistical significance.

The random effects model used for the NMA fit well, with a residual deviance of 27.23 reported. This corresponds well to the total number of trial arms, 27. No inconsistencies were identified in this network.

Based on the results of the NMA (in grey in table 7), tolerability assessed by withdrawal due to adverse events favours lamotrigine over carbamazepine, gabapentin over carbamazepine, lamotrigine over phenytoin and gabapentin over clonazepam. Table 8 presents the relative risk of each intervention compared to carbamazepine. It also gives the probability that each intervention is most effective.

Table 8: Tolerability of interventions in network 2 compared to carbamazepine

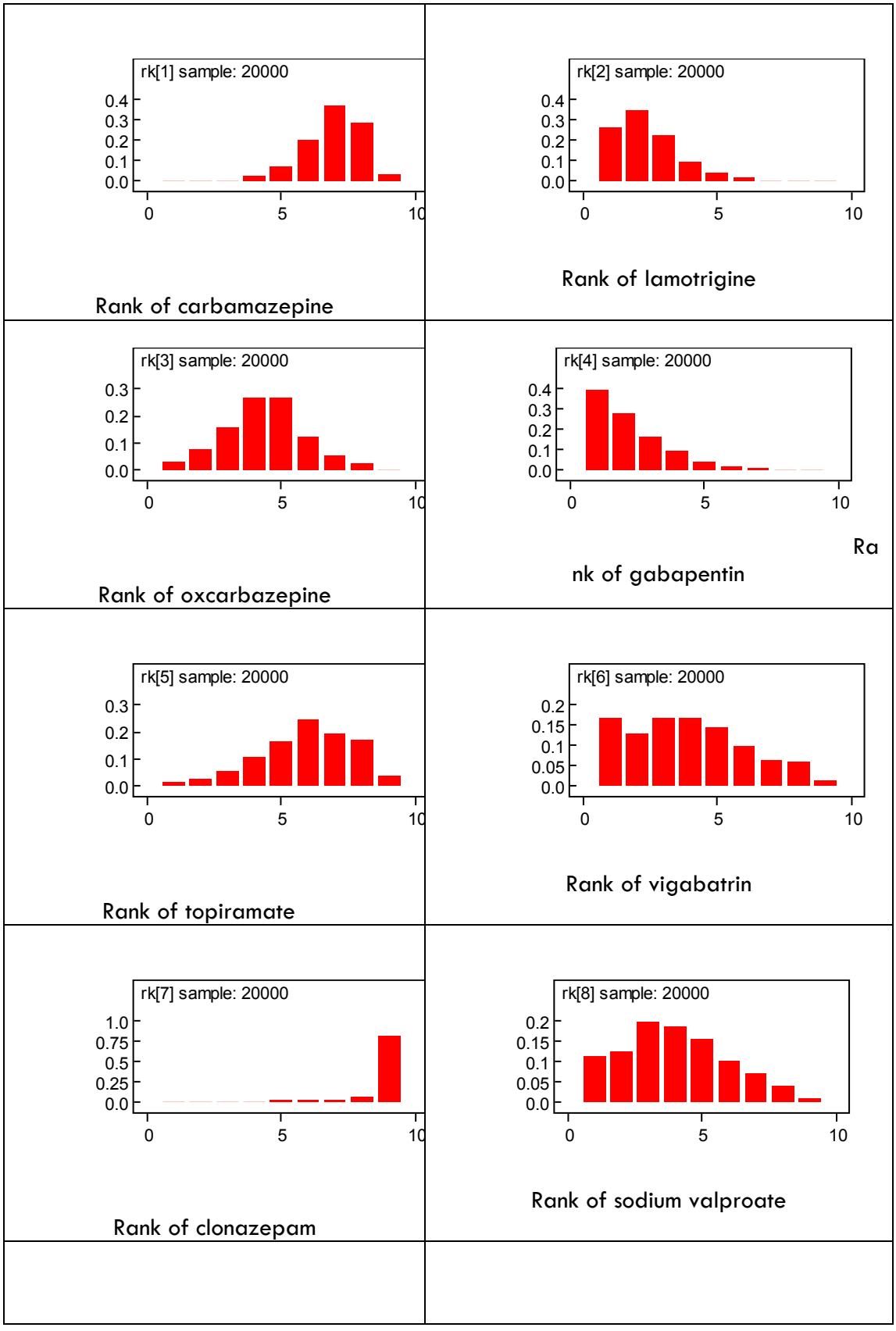
AED*	**^Median relative risk (95% Credible Interval)**	**Probability intervention is most tolerable (%)**
Carbamazepine	-	**0.03%**
Lamotrigine	**0.55 (0.29, 0.91)**	**26.3%**
Oxcarbazepine	0.74 (0.35, 1.24)	3.2%
Gabapentin	**0.53 (0.26, 0.90)**	**39.6%**
Topiramate	0.90 (0.41, 1.57)	1.5%
Vigabatrin	0.68 (0.26, 1.32)	16.5%
Clonazepam	1.97 (0.58, 3.48)	1.1%
Valproate	0.68 (0.29, 1.35)	11.3%
Phenytoin	1.02 (0.51, 1.75)	0.3%

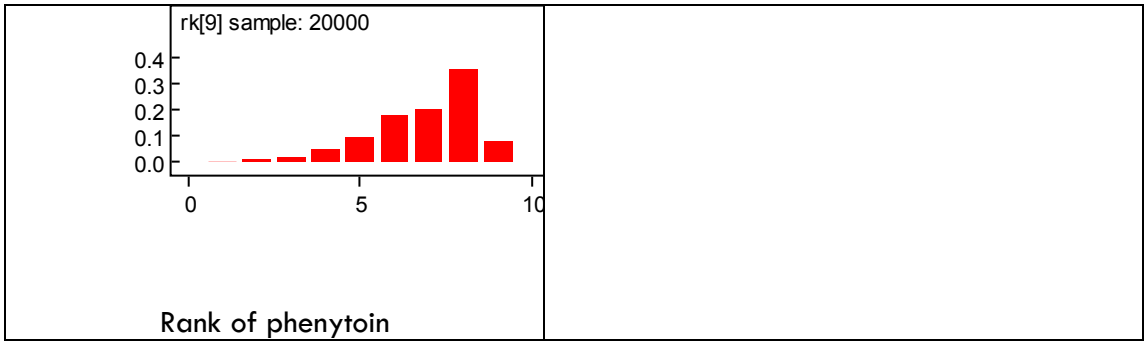
^ Median RR<1, Carbamazepine was less tolerable compared to the AED
SANAD data dichotomized from time to 12 month remission (year 1) to seizure freedom.

Based on point estimates, distribution of rank and proportion of simulations in which they are the most tolerable AEDs, gabapentin and lamotrigine were the most tolerable AEDs with a probability of 39.6% and 26.3% respectively

Figure 4 shows the distribution of probabilities of each intervention being ranked at each of 9 positions.

Figure 4: Ranking of interventions in network 2





Network 3: Adjunctive therapy for refractory focal seizures- 50% reduction in seizure frequency

Table 9 summarises the results of the conventional meta-analyses in terms of odds ratios generated from studies directly comparing different interventions. Table 9 also presents the results of the NMA in terms of odds ratios for every possible treatment comparison.

Table 9: Effectiveness (50% reduction in seizure frequency) of interventions in an adjunctive population with focal seizures, results of conventional and network meta-analyses

	2.70 (1.45-5.03)	**4.45 (2.61, 7.58)**	**2.65 (1.74-4.05)**	**3.90 (2.90-5.23)**	**4.50 (3.22-6.29)**	**4.45 (2.75-7.20)**	**4.45 (3.25-6.08)**	**1.88 (1.35, 2.63)**	**2.47 (1.80-3.40)**	**2.83 (1.99-4.01)**	1.84 (0.95-3.55)	**2.18 (1.26-3.79)**	**4.00 (2.35-6.81)**			
4.46 (2.31-9.76)			0.30 (0.06-1.68)										0.74 (0.23-2.27)			
4.72 (2.62-8.69)	1.06 (0.41-2.56)		0.62 (0.28-1.38)													
2.60 (1.62-4.21)	0.58 (0.25-1.27)	0.55 (0.28-1.07)												2.63 (0.41-16.66)		
3.97 (2.65-6.05)	0.89 (0.37-1.97)	0.84 (0.40, 1.74)	1.54 (0.81-2.90)													
5.26 (3.43-8.59)	1.18 (0.50-2.60)	1.11 (0.54, 2.44)	**2.02 (1.07-4.09)**	1.33 (0.73-2.53)												
4.54 (1.95-10.85)	1.02 (0.32-2.94)	0.97 (0.33, 2.76)	1.75 (0.66-4.80)	1.15 (0.44-2.97)	0.87 (0.31-2.24)											
4.48 (2.89-7.17)	1.01 (0.40-2.21)	0.95 (0.45-2.02)	1.73 (0.90-3.36)	1.13 (0.62-2.13)	0.85 (0.44-1.57)	0.99 (0.37-2.65)										
1.93 (1.06-3.56)	0.44 (0.16-1.06)	**0.40 (0.17, 0.95)**	0.74 (0.34-1.63)	0.49 (0.24-1.01)	**0.37 (0.17, 0.75)**	0.42 (0.15-1.21)	**0.43 (0.20-0.92)**									
2.54 (1.28-5.09)	0.57 (0.19-1.46)	0.54 (0.21, 1.32)	0.98 (0.42-2.24)	0.64 (0.29-1.42)	0.48 (0.20-1.05)	0.56 (0.18-1.64)	0.56 (0.25-1.27)	1.31 (0.53-3.23)								
2.83 (1.73-4.70)	0.63 (0.26-1.43)	0.60 (0.27-1.31)	1.09 (0.54-2.18)	0.72 (0.37, 1.36)	0.54 (0.27-1.02)	0.62 (0.23-1.67)	0.63 (0.32-1.22)	1.46 (0.67-3.20)	1.11 (0.48-2.59)							

1.83 (0.71-4.91)	0.41 (0.12-1.29)	0.39 (0.13-1.21)	0.71 (0.25-2.09)	0.46 (0.16-1.32)	0.35 (0.12-1.00)	0.40 (0.11-1.48)	0.41 (0.14-1.19)	0.94 (0.31-3.00)	0.73 (0.23-2.36)	0.65 (0.23-1.93)						
2.21 (0.90-5.36)	0.50 (0.15-1.44)	0.47 (0.16-1.34)	0.85 (0.30-2.31)	0.55 (0.20-1.46)	0.42 (0.15-1.10)	0.48 (0.14-1.67)	0.49 (0.18-1.30)	1.15 (0.38-3.35)	0.87 (0.28-2.63)	0.78 (0.28-2.10)	1.20 (0.31-4.39)					
3.94 (2.11 - 7.48)	0.89 (0.38-1.89)	0.83 (0.35-1.96)	1.52 (0.69-3.33)	1.00 (0.46-2.11)	0.75 (0.33-1.61)	0.87 (0.30-2.51)	0.88 (0.40-1.91)	2.05 (0.84-4.98)	1.55 (0.62-4.00)	1.40 (0.63-3.11)	2.16 (0.67-6.74)	1.78 (0.61-5.33)			**2.94 (1.38-6.25)**	1.36 (0.72-2.56)
7.80 (0.99-86.81)	1.83 (0.20-20.26)	1.70 (0.20-19.75)	3.12 (0.40-31.5)	2.02 (0.24-22.48)	1.51 (0.18-17.04)	1.76 (0.18-22.07)	1.79 (0.21-19.94)	4.11 (0.49-47.57)	3.20 (0.37-36.7)	2.85 (0.33-31.09)	4.44 (0.44-51.49)	3.62 (0.38-48.06)	2.05 (0.22-24.05)			
11.73 (3.62-38.66)	2.62 (0.71-8.99)	2.49 (0.66-9.20)	**4.51 (1.28-16.07)**	2.96 (0.84-10.41)	2.22 (0.62-7.78)	2.57 (0.61-11.22)	2.61 (0.73-9.29)	**6.06 (1.63-23.23)**	**4.65 (1.18-18.5)**	**4.14 (1.15-15.14)**	**6.33 (1.37-29.84)**	**5.32 (1.23-23.57)**	**2.95 (1.09-8.21)**	1.44 (0.10-15.82)		
5.35 (1.72-17.44)	1.2 (0.33, 4.04)	1.14 (0.31-4.07)	2.05 (0.61-7.22)	1.35 (0.40-4.73)	1.02 (0.28-3.43)	1.17 (0.28-5.03)	1.19 (0.35-4.09)	2.76 (0.76-10.58)	2.10 (0.57-8.30)	1.88 (0.55-6.83)	2.91 (0.65-13.51)	2.42 (0.59-10.8)	1.35 (0.53-3.54)	0.66 (0.04-7.3)	0.46 (0.11-1.83)	

Results in white are the odds ratios and 95% confidence intervals from the conventional meta-analyses of direct comparisons between the column-defining treatment and the row-defining treatment. Odds ratios greater than 1 favour the column-defining treatment.

Results in gray are the median odds ratios and credible intervals from the NMA of direct and indirect comparisons between the row-defining treatment and the column-defining treatment. Odds ratios greater than 1 favour the row-defining treatment.

Numbers in bold highlight statistically significant results (P<0.05).

Based on the direct comparisons (in white in table 9), lamotrigine, vigabatrin, gabapentin, levetiracetam, topiramate, oxcarbazepine, pregabalin, lacosamide, eslicarbazepine, zonisamide, lamotrigine XR, tiagabine were more effective in reducing 50% seizure frequency when compared individually to placebo. Lastly, carbamazepine was more effective in reducing 50% seizure frequency compared to tiagabine.

The random effects model used for this NMA fit reasonably well, with a residual deviance of 109.9 reported. This corresponds well to the total number of trial arms, 104.

Based on the results of the NMA (in grey in table 9), lamotrigine, vigabatrin, gabapentin, levetiracetam, topiramate, oxcarbazepine, pregabalin, lacosamide, eslicarbazepine, zonisamide, tiagabine, carbamazepine and phenytoin were more effective in reducing at least 50% seizure frequency when compared individually to placebo. Lacosamide was less effective when compared to vigabentin, topiramate and pregabalin. Topiramate was also more effective than gabapentin and carbamazepine was more effective compared to lacosamide, eslicarbazepine, zonisamide, levetiracetam and lamotrigine extended release and tiagabine.

Table 10 presents the relative risk of each intervention compared to no treatment (placebo). It also gives the probability that each intervention is the most effective.

Table 10: Probability of achieving 50% reduction in seizure frequency by using one of the following AEDs compared to no treatment (placebo)

AED*	^Median relative risk (95% Credible Interval)	Probability intervention is most effective (%)
Placebo		0
Lamotrigine	**2.94 (1.93, 4.21)**	1.17%
Vigabatrin	**3.03 (2.11, 4.04)**	1.15%
Gabapentin	**2.09 (1.48, 2.84)**	0.%
Levetiracetam	**2.75 (2.13, 3.44)**	0.125%
Topiramate	**3.21 (2.51, 4.02)**	1.89%
Oxcarbazepine	**2.97 (1.70, 4.38)**	2.98%
Pregabaline	**2.95 (2.25, 3.72)**	0.051%
Lacosamide	**1.70 (1.05, 2.57)**	0.%
Eslicarbazepine	**2.07 (1.23, 3.14)**	0.05 %
Zonisamide	**2.22 (1.56, 3.03)**	0.001%
Levetiracetam XR	1.63 (0.74, 3.10)	0.005%
Lamotrigine XR	1.87 (0.92, 3.24)	0.013%
Tiagabine	**2.74 (1.81, 3.79)**	0%
Valproate	**3.90 (0.99,6,26)**	**35%**
Carbamazepine	**4.50 (2.60,5.81)**	**51.2%**
Phenytoin	**3.24 (1.55, 5.03)**	5.7%

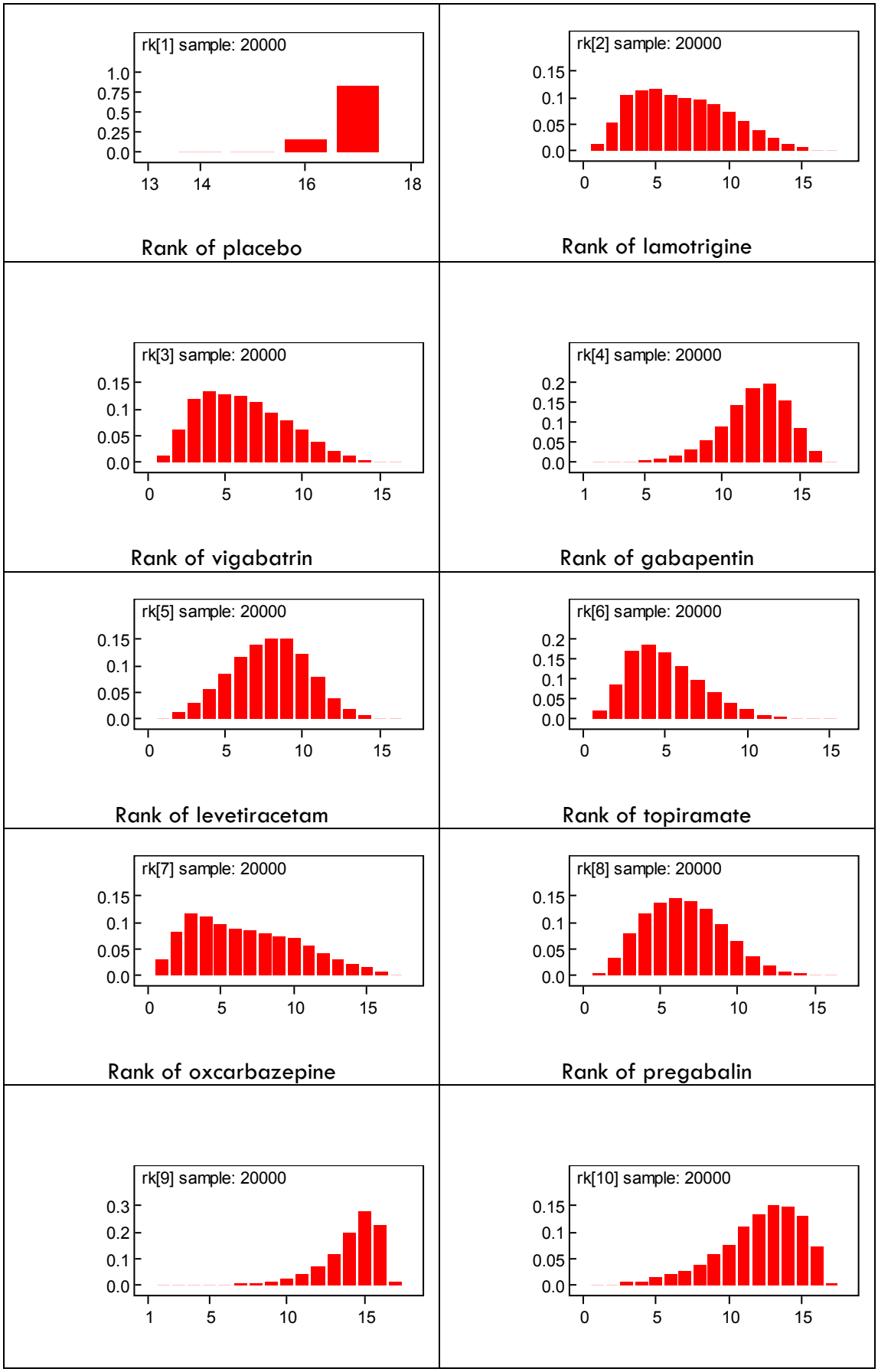
*compared against the placebo

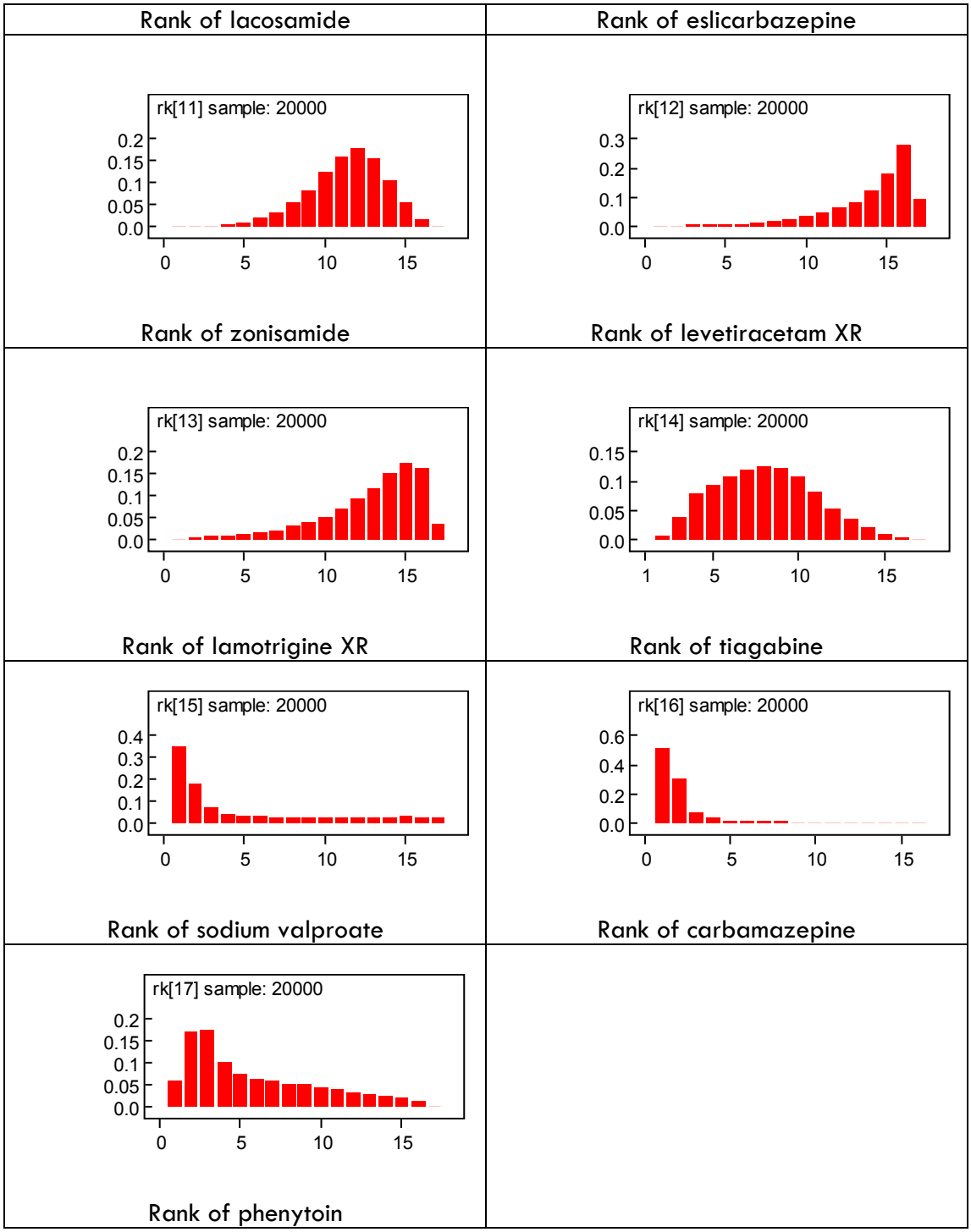
^ Median RR>1, AED was more effective compared to placebo

Based on point estimates, distribution of rank and proportion of simulations in which they are the most effective AEDs, carbamazepine and valproate were the most effective in achieving a reduction of at least 50% seizure frequency , with a probability of 51.2% and 35% respectively.

Figure 5 shows the distribution of probabilities of each intervention being ranked at each of 17 positions.

Figure 5: Ranking of interventions in network 3





Network 4: Adjunctive therapy for refractory focal seizures- withdrawal due to adverse events

Table 11 summarises the results of the conventional meta-analyses in terms of odds ratios generated from studies directly comparing different interventions. Table 11 also presents the results of the NMA in terms of odds ratios for every possible treatment comparison.

1 Figure 11: Tolerability (withdrawal due to adverse events) of adjunctive treatment in refractory focal seizures, results of conventional and network
2 meta-analyses

	7.17 (0.37-140.14)	**6.56 (3.76-11.47)**	**3.38 (2.16-5.30)**	**2.77 (1.58-4.87)**	**2.82 (1.53-5.20)**	**2.93 (1.70-5.04)**	**4.65 (2.22-9.74)**	**14.85 (3.42-64.38)**	2.60 (0.49-13.83)	6.05 (0.28-131.25)	0.89 (0.07, 10.77)	**3.34 (1.86-5.98)**	1.67 (0.92, 3.04)	1.40 (0.85-2.31)	**2.33 (1.11-4.91)**	**4.04 (1.48-10.99)**
25.89 (1.18-155.7)																
6.80 (2.66-17.54)	0.27 (0.03-6.64)															
3.65 (1.55-6.57)	0.14 (0.02-3.25)	0.54 (0.18-1.65)														
3.06 (1.55-6.67)1	0.12 (0.02-2.88)	0.45 (0.14, 1.52)	0.84 (0.33-2.14)													
2.91 (1.33-6.78)	0.11 (0.02-2.69)	0.43 (0.13-1.53)	0.79 (0.30-2.18)	0.95 (0.32-2.83)												
1.89 (0.73-5.27)	0.08 (0.01-1.82)	0.28 (0.07, 1.09)	0.52 (0.17-1.65)	0.62 (0.19-2.09)	0.65 (0.18-2.34)											
5.09 (2.11-14.42	0.20 (0.03-5.04)	0.75 (0.21-3.91)	1.39 (0.49-4.53)	1.65 (0.52-5.88)	1.71 (0.55-6.61)	2.67 (0. 71-11.22)										
7.73 (1.62-66.96	0.33 (0.02-12.28)	1.14 (0.18, 11.61)	2.09 (0.39-19.37)	2.54 (0.43-24.46)	2.67 (0.46, 25.85)	4.03 (0.65-39.18)	1.57 (0.23-14.52)									
2.69 (0.51-23.7)	0.11 (0.01-5.30)	0.39 (0.06, 4.32)	0.73 (0.12-6.78)	0.87 (0.15-8.78)	0.93 (0.15-9.63)	1.41 (0.21-14.75)	0.54 (0.08-5.28)	0.36 (0.02-5.37)								
22.9 (0.76-155.9)	0.94 (0.02-34.85)	3.33 (0.09-29.72)	6.21 (0.21-48.19)	7.28 (0.22, 59.44)	**7.72** (0.23-64.0)	11.83 (0.35-108.2)	4.29 (0.12-42.14)	2.60 (0.05-38.58)	7.54 (0.16-112.4)							
0.67 (0.18-	**0.03 (0.00-**	**0.10 (0.02-**	**0.19 (0.04-**	**0.22 (0.05-**	**0.23 (0.05-**	0.36 (0.07-	**0.13 (0.02-**	**0.08 (0.01-**	0.24 (0.02-	0.03 (0.00-		3.25 (0.98-			6.50 (0.94-	

2.08)	**0.66)**	**0.42)**	**0.64)**	**0.82)**	**0.92)**	1.56)	**0.56)**	**0.60)**	1.83)	1.06)		10.72)			45.11)	
3.16 (1.86-5.64)	**0.12 (0.02-0.66)**	0.46 (0.16-1.41)	0.86 (0.40-1.91)	1.02 (0.43-2.56)	1.08 (0.41-2.89)	1.65 (0.54-5.09)	0.62 (0.20-1.73)	0.41 (0.04-2.15)	1.19 (0.12-6.73)	0.14 (0.02-4.44)	4.60 (1.56-17.2)		0.79 (0.40-1.55)			
1.95 (1.13-3.45)	0.08 (0.01-1.80)	**0.28 (0.10-0.89)**	0.53 (0.24-1.18)	0.63 (0.26-1.58)	0.67 (0.25-1.80)	1.02 (0.33-3.17)	0.38 (0.12-1.09)	0.25 (0.03-1.35)	0.73 (0.08-4.26)	0.09 (0.01-2.82)	2.84 (0.87-11.5)	0.61 (0.33-1.18)		1.81 (0.89-3.70)		
1.88 (1.05 - 3.34)	0.07 (0.01-1.70)	**0.28 (0.09-0.81)**	0.52 (0.22-1.11)	0.62 (0.23-1.47)	0.65 (0.23-1.65)	1.00 (0.31-2.98)	0.37 (0.11-1.12)	0.24 (0.03-1.31)	0.71 (0.07-4.03)	0.08 (0.01-2.53)	2.77 (0.79-11.0)	0.60 (0.26-1.20)	0.98 (0.47-1.84)			
2.41 (1.22-4.80)	0.09 (0.01, 2.25)	0.35 (0.11-1.13)	0.66 (0.26-1.60)	0.78 (0.28-2.07)	0.82 (0.29-2.35)	1.26 (0.37-4.12)	0.48 (0.13-1.45)	0.31 (0.03-1.77)	0.91 (0.09-5.35)	0.11 (0.01-3.31)	3.56 (1.04-13.52)	0.78 (0.32-1.75)	1.26 (0.52-2.89)	1.28 (0.54-3.14)		0.95 (0.00-2.94)
4.39 (1.70-11.2)	0.17 (0.02-4.12)	0.64 (0.17-2.43)	1.22 (0.38-3.54)	1.45 (0.42-4.58)	1.51 (0.42-5.19)	2.34 (0.56-9.05)	0.85 (0.21-3.21)	0.57 (0.05-3.58)	1.65 (0.15-10.65)	0.19 (0.02-6.38)	6.62 (1.51-30.91)	1.42 (0.45-4.00)	2.29 (0.72-6.58)	2.36 (0.75-7.14)	1.82 (0.66-4.72)	

- Results in white are the odds ratios and 95% confidence intervals from the conventional meta-analyses of direct comparisons between the column-defining treatment and the row-defining treatment. Odds ratios greater than 1 favour the row- defining treatment (lower proportion of participants withdrawn due to adverse events).
- Results in gray are the median odds ratios and 95% credible intervals from the NMA of direct and indirect comparisons between the row-defining treatment and the column-defining treatment. Odds ratios greater than 1 favour the column- defining treatment (lower proportion of participants withdrawn due to adverse events).
- Numbers in bold highlight statistically significant results ($P<0.05$).

Based on the direct comparisons (in white in table 11), oxcarbazepine, pregabalin, tiagabine, lacosamide, eslicarbazepine, zonisamide, lamotrigine extended release, topiramate, gabapentin and vigabatrin were less tolerable as assessed by withdrawal due to adverse events when compared to no treatment (placebo).

The random effects model used for this NMA fit reasonably well, with a residual deviance of 121.2 reported. This corresponds reasonably well to the total number of trial arms 117.

Based on the results of the NMA (in grey in table 11) clobazam, oxcarbazepine, pregabalin, tiagabine, lacosamide, eslicarbazepine, zonisamide, lamotrigine extended release, topiramate, lamotrigine, levetiracetam, gabapentin and vigabatrin were significantly less tolerable compared to placebo. Valproate in the NMA analysis was found to be more tolerable when compared individually to clobazam, oxcarbazepine, pregabalin, tiagabine, lacosamide, zonisamide and lamotrigine extended release. Topiramate was also more tolerable as defined by a lower proportion of withdrawals due to adverse events compared to clobazam. Lastly, oxcarbazepine was less tolerable when compared to lamotrigine and levetiracetam.

No inconsistency was identified between the direct and NMA analysis results between the comparisons of any adjunctive treatment.

Table 12 presents the relative risk of each intervention compared to a baseline risk of no treatment (placebo). It also gives a probability of the intervention that an intervention has the highest risk of withdrawal due to adverse events (or least tolerable). Based on point estimates, distribution of rank and proportion of simulations in which they are the most tolerable AEDs, valproate was the most tolerable, with a probability of 66.7%.

Table 12: Probability of withdrawal due to adverse events by using one of the following AEDs compared to no treatment (placebo)

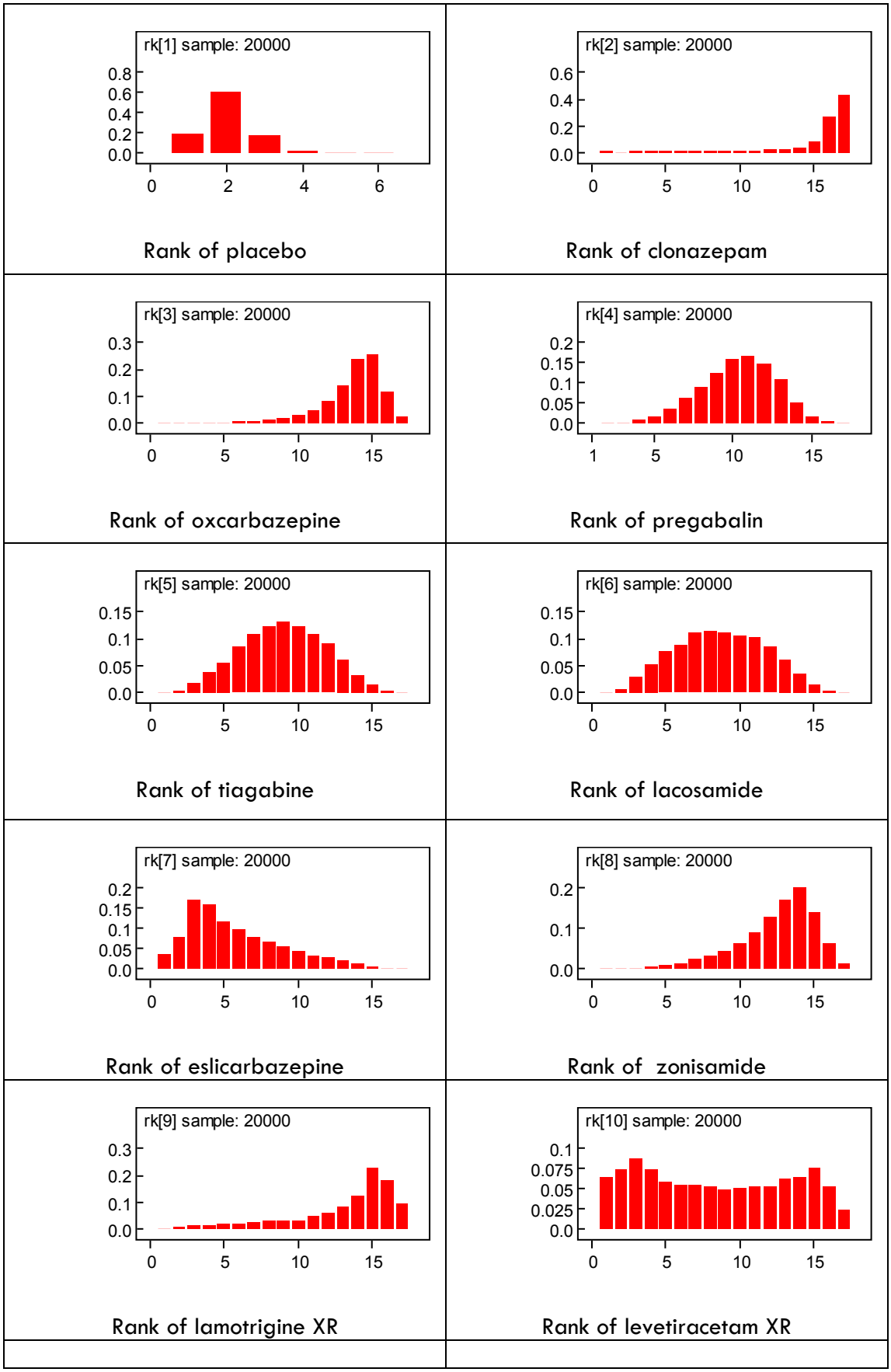
AED*	Median RR^	Upper CI
		Probability intervention is most tolerable (%)
Placebo		20%
Clobazam	**12.81 (1.17, 21.2)**	0.9%
Oxcarbazepine	**5.49 (2.49, 10.45)**	0.0012%
Pregabalin	**3.29 (2.02, 5.40)**	0%
Tiagabine	**2.82 (1.52, 5.34)**	0.005%
Lacosamide	**2.70 (1.31, 5.49)**	0.16%
Eslicarbazepine	1.83 (0.74, 4.48)	3.1%
Zonisamide	**4.36 (2.02, 9.30)**	0.0005%
Lamotrigine XR	**6.06 (1.58, 18.08)**	0.17%
Levetiracetam XR	2.52 (0.52, 12.27)	6.0%
Felbamate	12.07 (0.77, 21.21)	2.0%
Valproate	0.69 (0.19, 2.00)	66.7%
Topiramate	**2.90 (1.79, 4.74)**	0
Lamotrigine	**1.87 (1.12, 3.13)**	0.17%
Levetiracetam	**1.81 (1.05, 3.05)**	0.36%
Gabapentin	**2.28 (1.21, 4.16)**	0.0067%
Vigabatrin	**3.86 (1.64, 7.90)**	0.0025%

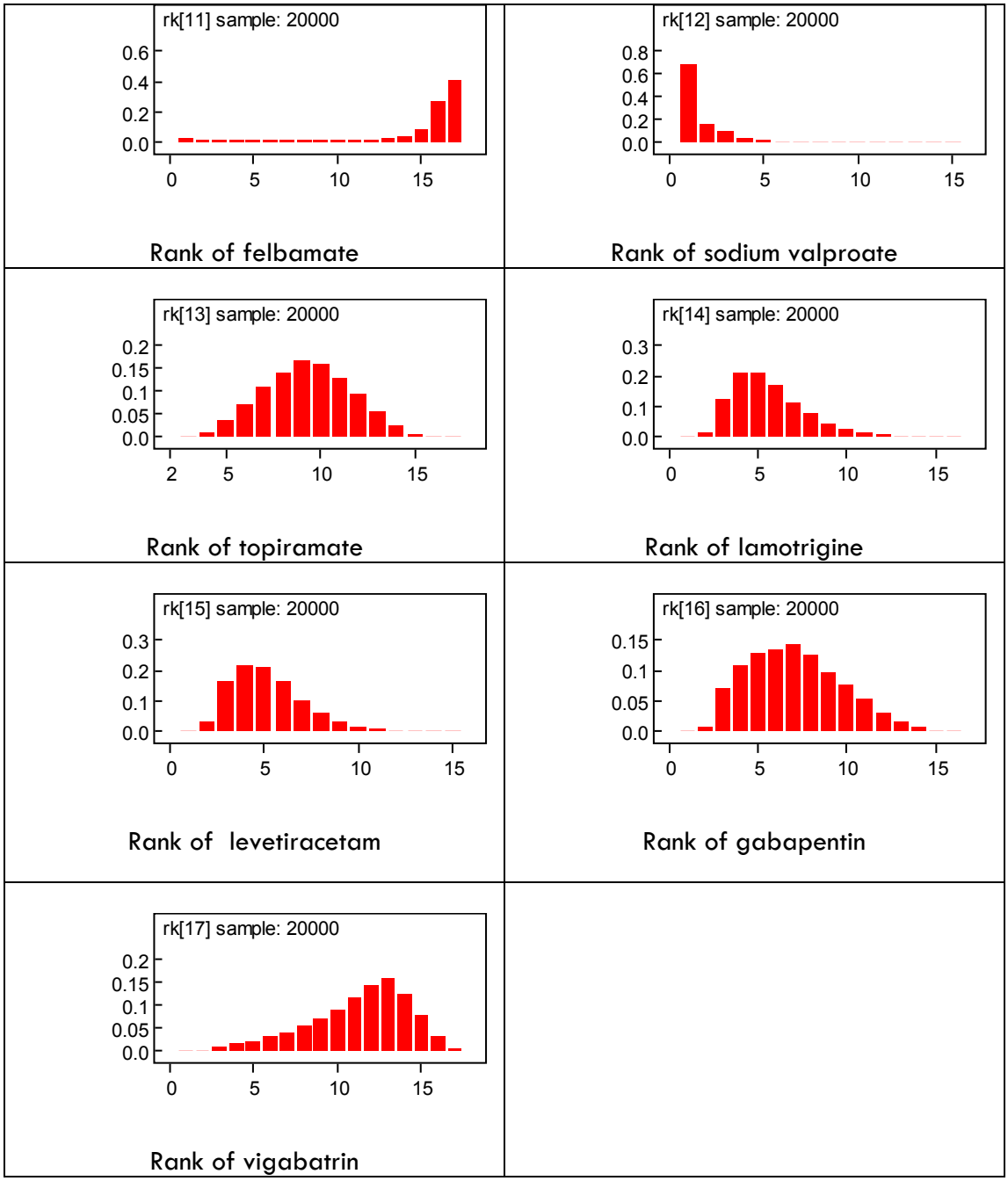
*compared against the placebo
^ Median RR>1, AED was less tolerable compared to placebo

Clobazam, oxcarbazepine, pregabalin, tiagabine, lacosamide, zonisamide, lamotrigine extended release, topiramate, lamotrigine, levetiracetam, gabapentin and vigabatrin were all found to be significantly less tolerable in relation to withdrawals due to adverse events compared to no treatment (placebo).

Figure 6 shows the distribution of probabilities of each intervention being ranked at each of 17 positions.

Figure 6: Ranking of interventions in network 4





The intention of reporting this outcome is to find out what is the proportion of patients assigned (or prescribed with) a drug would withdraw due to adverse events.Therefore, the number of patients randomised was used as the denominator in our data extraction for all parallel studies, except when the number of patients randomised were not reported in the studies reviewed. In these situations other figures which could be used as the denominator may be available (for example, "per protocol analysis" or "safety population"), depending on the statistical analysis plan of the studies. In these

situations, the largest number available were be used as the denominator for withdrawal due to adverse events.

Based on the same principle, the number of patients entering each phase of the trial was used as the denominator whenever possible in cross over trials. However, there were instances where this information was not available, and the number of patients participating in the study was used. There was a concern that in cross over trials where the timing of drop outs are not clearly reported, there wasa risk of bias from imputing number of patients randomised as the denominator; particularly when drop out rates are high, or unbalanced If more participants from one of the arms withdrew in phase I, there will be fewer participants available to cross over to the second phase of the trial. Therefore, there will be fewer patients exposed to the drug with less withdrawals compared to the drug with more withdrawals. This could inflate the difference in proportion of patients dropping out between the two arm and may affect conclusions.. Therefore, sensitivity analysis was conducted to test the robustness of including cross over trials in the NMA. The following scenarios were tested in a sensitivity analysis:

1. Including all cross over studies, regardless of drop out rates (base case)
2. Excluding cross over studies with >20% drop outs
3. Excluding cross over studies with >10% drop outs
4. Including only parallel studies, excluding any cross-over studies

Using 80,000 burn-in and 40,000 simulations (simulation was conducted until MC error/SD was 5% or less), we found no important difference in the results between all the scenarios in goodness of fit [83]and discrepancy or consistency of results [84,85]. Therefore, the results from the base case analysis were used.

1.4 Discussion

Based on the results of conventional meta-analyses of direct evidence, as has been previously presented in chapter 10 and appendix N, deciding upon the most effective intervention for the monotherapy and adjunctive treatment in focal seizures for newly diagnosed and refractory population is difficult. First, most interventions have not

been directly compared to one another in a randomised controlled trial and second, there are many instances of overlapping comparisons that could potentially give inconsistent estimates of effect. In order to overcome the difficulty of interpreting the conclusions from these numerous separate comparisons and to identify any inconsistency within estimated treatment effects, NMA of the direct evidence were performed.

Our analyses were based on a total of 86 studies, randomised to 19 different interventions used for monotherapy and adjunctive treatment. These studies formed four networks of evidence, which were differentiated by seizure type and outcome. The first two networks were formed using data from studies that included only newly diagnosed focal seizures. The first network was used to assess effectiveness of monotherapy in achieving seizure freedom and the second network was used to evaluate tolerability of monotherapy as defined by the proportion of people withdrawing due to adverse events. The third and fourth networks were formed using the data from the studies including refractory focal seizures; the third network was used to assess effectiveness of adjunctive treatment in achieving at least 50% reduction in seizure frequency, and, lastly, the fourth network evaluated tolerability as defined by the proportion of people withdrawing from adjunctive treatment due adverse events. The findings from the NMA have been used to facilitate decision-making for the GDG such that they could develop recommendations directed to the monotherapy and adjunctive treatment for newly diagnosed and refractory focal seizures in an adult population respectively, based on the best available direct and indirect evidence.

In the first network of monotherapy for assessing seizure freedom in newly diagnosed population, no AED (lamotrigine, oxcarbazepine, gabapentin, topiramate, vigabatrin, valproate and phenytoin) was found to be significantly different in terms of efficacy compared to carbamazepine.

In the second network of monotherapy assessing tolerability as defined by the proportion of people withdrawing due to adverse events, both lamotrigine and gabapentin were more tolerable when compared to carbamazepine. Although the analysis was able to generate probabilities of a given intervention being the best treatment, defined as having the greatest relative risk compared to baseline drug, carbamazepine in this case, the probability estimates illustrate the considerable uncertainty around which intervention is truly optimal. For example, gabapentin comes

out as the treatment with the lowest relative risk compared to carbamazepine for withdrawing due to adverse event but it is only the best tolerable in 39.6% of simulations. This means that some other intervention or interventions are best in 60.4% of simulations.

Similarly, when examining the results from the third network on adjunctive treatment for assessing the proportion of people achieving at least 50% reduction in seizure frequency, several AEDs (lamotrigine, vigabatrin, gabapentin, levetiracetam, topiramate, oxcarbazepine, pregabalin, lacosamide, eslicarbazepine, zonisamide, tiagabine and phenytoin) were found to be significantly more effective than placebo. However, for some of these AEDs, for example lacosamide and gabapentin, the probability of being the most effective treatment was as low as 0.%. The two most effective AEDs in achieving a reduction of at least 50% seizure frequency, based on point estimates, distribution of rank and proportion of simulations, were carbamazepine and valproate, with a probability of 51.2% and 35% respectively.

In the fourth network, all AEDs found to be significantly less tolerable than placebo in conventional meta-analysis were confirmed also in NMA, namely oxcarbazepine, pregabalin, tiagabine, lacosamide, eslicarbazepine, zonisamide, lamotrigine extended release, topiramate, gabapentin and vigabatrin. Clobazam and levetiracetam were found to be significantly less tolerable than placebo only in the NMA, with valproate found to be the most tolerable in a probability of 66.7%.

All four networks seem to fit well, as demonstrated by residual deviance and no inconsistencies in the networks were found.

In summary, there are several outcome measures that could be used to evaluate the effectiveness of different interventions used in the treatment of focal seizures, but only two were used in this analysis: proportion of people achieving seizure freedom in a newly diagnosed population and the proportion of people achieving at least 50% reduction in seizures. Dichotomous outcomes such as these were easier to evaluate and interpret and ultimately were easier to feed into the cost-effectiveness analysis conducted as part of the guideline development.

In addition to summarising the direct evidence into single measures of relative risk compared to no treatment, another aim of the NMA was to inform the effectiveness parameters in the economic model built to evaluate the cost-effectiveness of different

AEDs used as monotherapy and adjunctive therapy in the treatment of focal epilepsy. Although not all of the interventions included in the NMA were included in the economic model, they collectively formed a network of evidence that was used to derive the best estimates of effect for those interventions that were included in the model.

A cost-effectiveness analysis (CEA) may be deterministic or probabilistic. If it is deterministic then only the point estimates for the effect sizes are used in the CEA. If it is probabilistic, a distribution will be used for each effect size instead of a point estimate. A probabilistic cost-effectiveness analysis is based on simulations as is the NMA.

The median estimates of relative risk from the network meta-analysis for effectiveness (assessed by seizure freedom in newly diagnosed focal seizures and by at least 50% reduction in seizure frequency in refractory focal seizures) and tolerability (assessed by withdrawal due to adverse events in both populations) were used in the deterministic cost-effectiveness analysis (presented in appendix P). For the probabilistic sensitivity analysis, we took the 20,000 sets of odds ratios from the network meta-analysis and we then sampled from this 'data' set for each of 10,000 Monte Carlo simulations. In each probabilistic simulation, a set of odds ratios were selected (one for each intervention) from the same NMA simulation, thereby preserving the joint posterior distributions and incorporating all uncertainty and correlation of treatment effects.

1.5 Conclusion

Overall, the results of all four networks, for monotherapy and adjunctive treatment, showed that carbamazepine and valproate are among the most effective AEDs for the treatment of newly diagnosed and refractory focal seizures. The first network for newly diagnosed focal seizures demonstrated that no AED was significantly more effective than carbamazepine in achieving seizure freedom. However, valproate and phenytoin ranked as the most effective AEDs in achieving seizure freedom with a probability of 38.5% and 33.9% respectively. Gabapentin and lamotrigine were the most tolerable AEDs with a probability of 39.6% and 26.3% respectively.

In refractory focal seizures, most AEDs were significantly more effective in reducing at least 50% seizure frequency compared to placebo. Carbamazepine and valproate were the most effective adjunctive AEDs in achieving a reduction of at least 50% seizure frequency, with a probability of 51.2% and 35% respectively.

For withdrawal due to adverse events, most of the AEDs were significantly less tolerable compared to placebo, with valproate found to be the most tolerable in a probability of 66.7%.

WinGUGS codes for the random effects model for the monotherapy treatment of focal seizures: multi-arm trials (any number of arms)

```
model{
for(i in 1:9){
        w[i,1] <-0
             delta[i,t[i,1]]<-0
             mu[i] ~ dnorm(0,.0001)                                    # vague priors
for trial baselines
             for (k in 1:na[i])  {
                  r[i,k] ~ dbin(p[i,t[i,k]],n[i,k])                    # binomial
likelihood
                              logit(p[i,t[i,k]])<-mu[i] + delta[i,t[i,k]]
                              # model
#Deviance residuals for data i
      rhat[i,k] <- p[i,t[i,k]] * n[i,k]
      dev[i,k] <- 2 * (r[i,k] * (log(r[i,k])-log(rhat[i,k]))  +  (n[i,k]-r[i,k]) * (log(n[i,k]-r[i,k]) -
log(n[i,k]-rhat[i,k])))
                  }

         sdev[i]<- sum(dev[i,1:na[i]])

                   for (k in 2:na[i]) {
              delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]],taud[i,t[i,k]])I(-5,5)          # trial-specific
LOR distributions
             md[i,t[i,k]] <-  d[t[i,k]] - d[t[i,1]]  + sw[i,k]              # mean of LOR
distributions
              taud[i,t[i,k]] <- tau *2*(k-1)/k                             #precision of LOR
distributions
              w[i,k] <- (delta[i,t[i,k]]  - d[t[i,k]] + d[t[i,1]])        #adjustment, multi-arm
RCTs
              sw[i,k] <-sum(w[i,1:k-1])/(k-1) }              # cumulative adjustment for
multi-arm trials
  }

d[1]<-0
for (k in 2:8){d[k] ~ dnorm(0,.0001) }                  #  vague priors for basic
parameters

sd~dunif(0,2)                                    #  vague prior for random effects
standard deviation
tau<-1/pow(sd,2)

A<-0.363
for (k in 2:8) {logit(T[k])<-logit(A)+d[k]}

rr[1]<-1
for (k in 2:8)  {logit(v[k])<-logit(0.363)+d[k]
rr[k]<-v[k]/0.363 }                          # calculate relative risk

sumdev <- sum(sdev[])                                                  # Calculate residual
deviance
```

```
# Ranking and prob{treatment k is best}
 for (k in 1:8) {
            rk[k]<-9-rank(rr[],k)
best[k]<-equals(rank(rr[],k),8)}


# pairwise ORs
for (c in 1:(8-1))
        {  for (k in (c+1):8)
             {  lor[c,k] <- d[k] - d[c]
                log(or[c,k]) <- lor[c,k]
             }
         }
}



# NT=no. treatments, NS=no. studies;
# NB : set up M vectors each r[,]. n[,] and t[,],  where M is the Maximum number of
treatments
#         per trial in the dataset. In this dataset M is 4.


# NT=8 NS=9  BR=0.363



list(
d=c(NA,1,2,3, 4,5,6,7), # one for each treatment
sd=1,
mu=c(1,2,3,4,5,  6,7,8,9) # one for each trial

)


)

list(
d=c(NA,0.1,-1,-0.2),
sd=.2,
mu=c(1,-1,-2,0,0,    -2,1,0,2,2,    1,-1,-2,0,0,   -2,1,0,2,2,   -2,-0.5,-3,0.5)
)
```

WinGUGS codes for the random effect model for the adjunctive treatment of focal seizures : includes correlation structure for 3-arm trials

```
model{
sw[1] <- 0
for(i in 1:104)  {
```

```
      logit(p[i])<-mu[s[i]]+ delta[i]  * (1-equals(t[i],b[i]))
#  model
      r[i]~dbin(p[i],n[i])                                                    #
binomial likelihood
       delta[i] ~ dnorm(md[i],taud[i])I(-5,5)                                 # trial-
specific LOR distributions
       taud[i] <- tau * (1 + equals(m[i],3) /3)                               # precisions of LOR
distributions
      md[i] <- d[t[i]] - d[b[i]]  +  equals(m[i],3) * sw[i]                   # means of LOR
distributions

#Deviance residuals for data i
      rhat[i] <- p[i] * n[i]
      dev[i] <- 2 * (r[i] * (log(r[i])-log(rhat[i]))  +  (n[i]-r[i]) * (log(n[i]-r[i]) - log(n[i]-
rhat[i])))

     }

sumdev <- sum(dev[])                                                          # Calculate residual
deviance


for (i in 2:104)  {   sw[i] <- (delta[i-1] -  d[t[i-1]] + d[b[i-1]])/2}       # adjustment
for 3-arm trials

for(j in 1:52){ mu[j]~dnorm(0,.0001) }                                        # vague priors for NS
trial baselines

d[1]<-0
for (k in 2:17)  {d[k] ~ dnorm(0,.0001) }                                     # vague priors for
basic parameters

sd~dunif(0,2)                                    #  vague prior for random effects
standard deviation
tau<-1/pow(sd,2)

rr[1]<-1
for (k in 2:17)  {logit(v[k])<-logit(0.150)+d[k]
rr[k]<-v[k]/0.150 }                              # calculate relative risk

# Ranking and prob{treatment k is best}
 for (k in 1:17) {
            rk[k]<-18-rank(rr[],k)
best[k]<-equals(rank(rr[],k),17)}

# Pairwise ORs
for (c in 1:(17-1))
        {  for (k in (c+1):17)
             {  lor[c,k] <- d[k] - d[c]
                log(or[c,k]) <- lor[c,k]
             }
         }
}
```

```
#initial 1
list(
d=c(NA,-0.5,-1,-0.2, 0,-0.5,-1,-0.2, 0,-0.5,-1,-0.2, 0,-0.5,-1,-0.2, 2), # one for each
treatment
sd=1.2,
mu=c(-2.2,-2.3,-2.4,-2.5,-2.6,  -2.2,-2.3,-2.4,-2.5,-2.6,  -2.2,-2.3,-2.4,-2.5,-2.6,  -
2.2,-2.3,-2.4,-2.5,-2.6,  -2.2,-2.3,-2.4,-2.5,-2.6, -2.2,-2.3,-2.4,-2.5,-2.6,  -2.2,-2.3,-
2.4,-2.5,-2.6,  -2.2,-2.3,-2.4,-2.5,-2.6,  -2.2,-2.3,-2.4,-2.5,-2.6,  -2.2,-2.3,-2.4,-
2.5,-2.6,  -2.2,-2.3), # one for each trial
delta=c(0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-
0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-
0.8,  0,-0.2,-0.4,-0.6,-0.8, 0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-
0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,
0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8, 0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-
0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6,-0.8,  0,-0.2,-0.4,-0.6) # one for each
data point
)

#initial 2
list(
d=c(NA,0,1,0), # one for each treatment
sd=.1,
mu=c(0,1,0,1,0,  -1,0,-1,0,-1,  0,1,0,1,0,  -1,0,-1,0,-1,  0,1,0,1),  # one for each
trial
delta=c(0,1,0,1,0,  -1,0,-1,0,-1,  0,1,0,1,0,  -1,0,-1,0,-1,  0,1,0,1,0,  -1,0,-1,0,-1,
0,1,0,1,0,  -1,0,-1,0,-1, 0,1,0,1) # one for each data point
)
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