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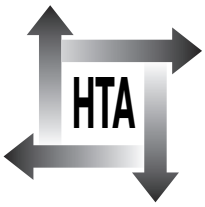

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NIHR Health Technology Assessment Programme

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The research reported in this monograph was commissioned by the HTA Programme as project number 95/13/01. The contractual start date was in September 1998. The draft report began editorial review in June 2006 and was accepted for publication in April 2007. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

A randomised controlled trial examining the longer-term outcomes of standard versus new antiepileptic drugs. The SANAD trial

AG Marson,[1] R Appleton,[2] GA Baker,[1] DW Chadwick,[1*] J Doughty,[3] B Eaton,[1] C Gamble,[4] A Jacoby,[5] P Shackley,[6] DF Smith,[7] C Tudur-Smith,[4] A Vanoli[6] and PR Williamson[4]

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Objectives: To compare clinicians' choice of one of the standard epilepsy drug treatments (carbamazepine or valproate) versus appropriate comparator new drugs.
Design: A clinical trial comprising two arms, one comparing new drugs in carbamazepine and the other with valproate.
Setting: A multicentre study recruiting patients with epilepsy from hospital outpatient clinics.
Participants: Patients with an adequately documented history of two or more clinically definite unprovoked epileptic seizures within the last year for whom treatment with a single antiepileptic drug represented the best therapeutic option.
Interventions: Arm A was carbamazepine (CBZ) versus gabapentin (GBP) versus lamotrigine (LTG) versus oxcarbazepine (OXC) versus topiramate (TPM). Arm B valproate (VPS) versus LTG versus TPM.
Main outcome measures: Time to treatment failure (withdrawal of the randomised drug for reasons of unacceptable adverse events or inadequate seizure control or a combination of the two) and time to achieve a 12-month remission of seizures. Time from randomisation to first seizure, 24-month remission of seizures, incidence of clinically important adverse events, quality of life (QoL) outcomes and health economic outcomes were also considered.
Results: Arm A recruited 1721 patients (88% with symptomatic or cryptogenic partial epilepsy and 10% with unclassified epilepsy). Arm B recruited 716 patients (63% with idiopathic generalised epilepsy and 25% with unclassified epilepsy). In Arm A LTG had the lowest incidence of treatment failure and was statistically superior to all drugs for this outcome with the exception of OXC. Some 12% and 8% fewer patients experienced treatment failure on LTG than CBZ, the standard drug, at 1 and 2 years after randomisation, respectively. The superiority of LTG over CBZ was due to its better tolerability but there is satisfactory evidence indicating that LTG is not clinically inferior to CBZ for measures of its efficacy. No consistent differences in QoL outcomes were found between treatment groups. Health economic analysis supported LTG being preferred to CBZ for both cost per seizure avoided and cost per quality-adjusted life-year gained. In Arm B for time to treatment failure, VPS, the standard drug, was preferred to both TPM and LTG, as it was the drug least likely to be associated with treatment failure for inadequate seizure control and was the preferred drug for time to achieving a 12-month remission. QoL assessments did not show any between-treatment differences. The health economic assessment supported the conclusion that VPS should remain the drug of first choice for idiopathic generalised or unclassified epilepsy, although there is a suggestion that TPM is a cost-effective alternative to VPS.

Conclusions: The evidence suggests that LTG may be a clinical and cost-effective alternative to the existing standard drug treatment, CBZ, for patients diagnosed as having partial seizures. For patients with idiopathic generalised epilepsy or difficult to classify epilepsy, VPS remains the clinically most effective drug, although TPM may be a cost-effective alternative for some patients. Three new antiepileptic drugs have recently been licensed in the UK for the treatment of epilepsy (levetiracetam, zonisamide and pregabalin), therefore these drugs should be compared in a similarly designed trial.

Contents

List of abbreviations

ABNAS	Aldenkamp Baker neuropsychological assessment schedule
AE	attitude to epilepsy
AED	antiepileptic drug
AEP	Adverse Events Profile
AUC	area under the curve
BNF	British National Formulary
CBC	Child Behaviour Checklist
CBZ	carbamazepine
CEAC	cost-effectiveness acceptability curve
CHQ	Child Health Questionnaire
CI	confidence interval
CL	confidence limit
df	degrees of freedom
EEG	electroencephalogram
EI	epilepsy impact
EVPI	expected value of perfect information
GBP	gabapentin
GQoL	global quality of life
HCHS	Hospital and Community Health Services
HR	hazard ratio
ICER	incremental cost-effectiveness ratio
ILAE	International League Against Epilepsy
IoE	impact of epilepsy (scale)
IPD	individual patient data
ISC	inadequate seizure control
ITT	intention-to-treat
LTG	lamotrigine
MRC	Medical Research Council
NEWQOL	Newly Diagnosed Epilepsy Quality of Life
NICE	National Institute for Health and Clinical Excellence
OXC	oxcarbazepine
PHB	phenobarbitone
PP	per-protocol
QALY	quality-adjusted life-year
QoL	quality of life
QOLIE-AD	Quality of Life in Epilepsy Inventory for Adolescents
RCT	randomised controlled trial
SANAD	Standard And New Antiepileptic Drugs
SEALS	Side Effects and Life Satisfaction
TPM	topiramate
UAE	unacceptable adverse event
VPS	valproate

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Epilepsy is a common disorder (prevalence 0.5–1%) that is associated with varied prognosis but with considerable consequences for quality of life (QoL) and costs for society. The primary form of treatment is pharmacological. Current National Institute for Health and Clinical Excellence (NICE) guidelines for the treatment of epilepsy identify carbamazepine and valproate as being first-choice treatments.

Objectives

The aims of the study were to compare clinicians' choice of one of the standard drug treatments (carbamazepine or valproate) versus appropriate comparator new drugs in patients who are managed with single drug treatment and to examine outcomes of treatment with regard to seizure recurrence, QoL impairments, chronic epilepsy and the cost-effectiveness of medical management strategies.

Design

The study was a pragmatic, randomised, unmasked, parallel group clinical trial comprising two arms, one comparing new drugs with carbamazepine and the other comparing new drugs with valproate.

Setting

This was a multicentre study recruiting patients with epilepsy from hospital outpatient clinics. At least 90% of new treatments of epilepsy would be expected to be initiated in this setting.

Participants

Patients with an adequately documented history of two or more clinically definite unprovoked epileptic seizures within the last year for whom treatment with a single antiepileptic drug represented the optimal therapeutic option were recruited. The study did not recruit children under the age of 5 years, those with acute symptomatic seizures or those who had a history of progressive neurological or medical disease.

Interventions

Arm A was carbamazepine (CBZ) versus gabapentin (GBP) versus lamotrigine (LTG) versus oxcarbazepine (OXC) versus topiramate (TPM) and Arm B valproate (VPS) versus LTG versus TPM. When clinicians felt that CBZ was the optimal standard drug, patients were allocated to Arm A, and when VPS was the optimal drug they were allocated to Arm B. In both arms, guidelines were given as to initial dosing, but choice of dose and variation in dose with seizure response and adverse events were at the discretion of the clinician.

Main outcome measures

Primary outcome measures

1. Time to treatment failure (withdrawal of the randomised drug for reasons of unacceptable adverse events or inadequate seizure control or a combination of the two).
2. Time to achieve a 12-month remission of seizures.

Secondary outcome measures

1. Clinical outcomes: time from randomisation to first seizure, 24-month remission of seizures, incidence of clinically important adverse events.
2. QoL outcomes.
3. Health economic outcomes.

Results

A total of 1721 patients were recruited to Arm A and 716 to Arm B. Arm A recruited 88% of patients with symptomatic or cryptogenic partial epilepsy and 10% with unclassified epilepsy. Arm B recruited 63% of patients with idiopathic generalised epilepsy and 25% with unclassified epilepsy.

Arm A

LTG had the lowest incidence of treatment failure and was statistically superior to all drugs for this outcome with the exception of OXC. Some 12% and 8% fewer patients experienced treatment failure on LTG than CBZ, the standard drug, at 1 and 2 years after randomisation, respectively. The superiority of LTG over CBZ was due to its better tolerability but there is satisfactory evidence indicating that LTG is not clinically inferior to CBZ for measures of its efficacy (treatment failure due to inadequate seizure control and time to achieving a 12-month remission). No consistent differences in QoL outcomes were found between treatment groups, although patients achieving a 12-month remission by 2 years after randomisation had superior QoL outcomes to those who had not, and patients who had experienced a treatment failure outcome exhibited poorer QoL than those who remained on their randomised treatment. Health economic analysis supported LTG being preferred to CBZ for both cost per seizure avoided and cost per quality-adjusted life-year gained.

Arm B

For time to treatment failure, VPS, the standard drug, was preferred to both TPM and LTG. VPS was the drug least likely to be associated with treatment failure for inadequate seizure control and was the preferred drug for time to achieving a 12-month remission. QoL assessments did not show any between-treatment differences, though patients achieving a 12-month remission by 2 years after randomisation had superior QoL outcomes to those who had not and patients who had experienced a treatment failure outcome exhibited poorer QoL. The health economic assessment supported the conclusion that VPS should remain the drug of first choice for idiopathic generalised or unclassified epilepsy, although there is a suggestion that TPM is a cost-effective alternative to VPS.

Conclusions

Implications for healthcare

The study provides evidence that LTG may be a clinical and cost-effective alternative to the existing standard drug treatment, CBZ. Some 88% of patients in Arm A were diagnosed as having partial seizures, so conclusions are applicable to patients with these epilepsy syndromes. For patients in Arm B with idiopathic generalised epilepsy or difficult to classify epilepsy, VPS remains the clinically most effective drug, although TPM may be a cost-effective alternative for some patients.

It should be noted that the SANAD trial was not designed to address the issue of safety during pregnancy, an important factor for choice of antiepileptic drugs in women during their childbearing years.

Recommendations for research

Since the design and start of the trial, three new antiepileptic drugs have been licensed in the UK for the treatment of epilepsy (levetiracetam, zonisamide and pregabalin). It will be important that these drugs are compared in a similarly designed trial with LTG and OXC and also with VPS.

Chapter 1
Introduction

Epilepsy is a common disorder (incidence 50 per 100,000; prevalence 0.5–1%.[1] Studies of the natural history of the condition indicate that as many as 70% of patients enter long-term remission shortly after starting drug therapy.[2,3] However, 20–30% of patients with existing treatment have a chronic and disabling epilepsy with considerable psychosocial consequences for the individual and costs for society.[4–6] Even groups of patients in remission of their epilepsy may be subject to dose-related side-effects and chronic toxicity from their antiepileptic drugs. The psychosocial consequences and the economic impact of these are less well defined.[7]

Currently in the UK, carbamazepine (CBZ) and valproate (VPS) are the first-line antiepileptic drug (AED) treatments, CBZ being effective against partial seizures (with or without secondary generalisation) and generalised tonic–clonic seizures, whereas VPS is effective against a broader range of seizure types and is the preferred treatment for generalised seizures.[8] A number of randomised controlled trials (RCTs) have compared these drugs and other older drugs.[9–13] Whereas the largest study suggested that CBZ may be more efficacious than VPS in preventing complex partial seizures in a population of people with partial epilepsy,[9] results of an individual patient data meta-analysis indicate that the two drugs are broadly similar, as measured by a practical outcome of effectiveness, retention time (time to treatment failure) on drug following randomisation, reflecting withdrawal either because of lack of efficacy or because of poor tolerability.[14]

In an attempt to summarise evidence regarding pair-wise drug comparisons of AEDs, separate Cochrane systematic reviews have been prepared, or are in preparation, in which the following comparisons are made: CBZ versus VPS,[15] phenytoin versus VPS,[16] CBZ versus phenytoin,[17] phenytoin versus phenobarbitone (PHB)[18] and CBZ vs PHB.[19] An individual patient data (IPD) approach was used in these reviews, meta-analysis being undertaken using full trial data sets, rather than published or aggregate level data. These reviews provide the best available evidence about the comparative effects of pairs of established AEDs. One important limitation is that in isolation, a pair-wise comparison does not inform a choice among all available drugs. A further limitation of existing RCT data is that not all available drugs have been compared head-to-head. In order to address some of these issues Tudur-Smith and colleagues have undertaken a more extensive meta-analysis of both direct and indirect evidence from monotherapy comparisons of established AEDs and two newer AEDs, lamotrigine (LTG) and oxcarbazepine (OXC) (personal communication). Individual patient data are available for 4516 patients randomised within 18 RCTs; 3115 patients (68%) had partial onset seizures, and for time to 12-month remission, results favour OXC and CBZ, but no data for LTG are available for this outcome. For time to first seizure, results favour PHB followed by OXC and CBZ. For time to treatment withdrawal, results favour OXC and LTG, and PHB is significantly worse than the other drugs. Of the two new AEDs, for patients with partial onset seizures the overall results favour OXC, and for the older AEDs, results favour CBZ. A total of 1331 patients (29%) were classified as having generalised onset tonic–clonic seizures, and for time to 12-month remission trends favour PHT followed by CBZ followed by VPS, whereas for time to first seizure, trends favour PHT followed by VPS followed by LTG. For time to treatment withdrawal, trends favour LTG followed by PHT followed by VPS. Results do not give a clear indication as to the drug of choice for patients with generalised onset tonic–clonic seizures, as the studies included smaller numbers of patients with this seizure type, and such patients were poorly and unreliably identified.

The last decade and a half has seen the licensing and introduction of a number of new AEDs. These have all been licensed initially on the basis of placebo-controlled add-on clinical trials in patients with refractory partial epilepsy. An aggregate data meta-analysis of these studies[20] indicated by indirect comparisons that some agents may be more effective than others, although no statistically significant differences were found. Some comparative studies of the new drugs compared to standard AEDs have appeared.[21–35] These studies are, however, short in duration, have

used different outcome measures, have not systematically addressed quality of life (QoL) outcomes and have not been structured to assess health economic issues. Although they may be valuable for licensing purposes for a monotherapy indication, they do not inform clinical practice in a sensible way, bearing in mind the chronic nature of epilepsy and its implications for long-term therapy and control. In spite of this, there has been a steady rise in the prescribing of new AEDs from 0.1% of total AED prescriptions in 1991 to 20% in 2002. New drugs accounted for 69% of the total costs of AEDs to the NHS (£99 million of £142 million).[36] These changes in practice will have important consequences when demands on scarce healthcare resources greatly exceed the ability of those resources to meet such demands. There is therefore a need for information on the cost-effectiveness of the new AEDs by undertaking an economic evaluation alongside the clinical trial where the comparative analysis of the alternative treatment strategies is undertaken in terms of their costs and consequences.[37]

Given that the majority of patients who develop epilepsy are treated with single drugs and may continue to take them for many years, it is essential that standard and new drugs are compared so as to establish which should, in the future, be first choice for appropriate groups of patients. The absence of evidence to inform the choice was emphasised in the National Institute for Health and Clinical Excellence (NICE) appraisals of new AEDs.[36,38]

It would be accepted that a new drug could become first choice if it is superior for both efficacy and tolerability/safety, compared with the existing standard. One could also argue that a new drug could become first choice if it is better tolerated and has been shown to have equivalent efficacy. We would need, however, to have confidence in the assessment of equivalence and the affordability of the benefits.

For these reasons, we have undertaken a study to compare clinicians' choice of current first-line treatment (CBZ or VPS) versus appropriate comparator new drugs [gabapentin (GBP), LTG, OXC and topiramate (TPM)] used as monotherapy, to examine seizure control, tolerability, QoL and health economic outcomes in two concurrent, pragmatic, randomised (unblinded) parallel group clinical trials.

Chapter 2
Methods

The study was commissioned and sponsored by the NHS R&D Health Technology Assessment Programme, but also supported by those pharmaceutical companies with drugs included in the study, who contributed approximately 20% of the total costs of the study. It received appropriate multicentre and local ethics and research committee approvals. Patients gave informed consent to inclusion and to long-term follow-up. The conduct of the trial was monitored by an independent Data Monitoring and Ethics Committee who had access to data by treatment group, and by a Trial Steering Committee following Medical Research Council (MRC) Good Clinical Practice Guidelines.[39]

Patients presenting to participating clinicians were cued for entry to the trial if they met inclusion criteria consisting of a history of two or more clinically definite unprovoked epileptic seizures in the previous year and if treatment with a single AED represented the best therapeutic option. This allowed inclusion of patients with newly diagnosed epilepsy, patients who had failed treatment with previous monotherapy (provided that the drug failure did not include one of the drugs present in the randomisation) and patients in remission of epilepsy, who had relapsed following withdrawal of treatment. Patients were excluded if the clinician or patient felt that treatment was contraindicated, if all their seizures had been acute symptomatic seizures (including febrile seizures), they were aged 4 years or younger or if there was a history of progressive neurological disease. Clinicians were strongly encouraged to provide anonymised baseline data for patients who were eligible but not randomised.

Information recorded at entry to the study included patient demographics, the presence of a history of learning disability or developmental delay, prior neurological history including head injury, stroke, intracerebral infection and acute symptomatic seizures, and a history of epilepsy in a first-degree family member. Clinicians were asked to classify seizures and epilepsy syndromes by International League Against Epilepsy (ILAE) classifications[40,41] as far as was possible, at least to differentiate between focal or generalised onset seizures. However, where there was uncertainty patients were recorded as having unclassified convulsive or other unclassified seizures. Results of any electroencephalogram (EEG) or brain imaging around the time of randomisation were recorded.

Participating clinicians were asked to consider which of the two standard AEDs, CBZ and VPS, was the most appropriate treatment for an individual patient. Where CBZ was chosen, patients entered Arm A of the study and were randomly allocated to treatment with CBZ, GBP, LTG, OXC or TPM in a ratio of 1:1:1:1:1. (OXC was only included in this randomisation after 1 June 2001, resulting in fewer patients being randomised to this drug.) Where VPS was chosen as standard drug, patients entered Arm B and randomisation was between VPS, LTG and TPM in a ratio of 1:1:1. Randomisation was by telephone using minimisation [with stratification by centre, sex and drug history (newly diagnosed and untreated, treated with ineffective monotherapy, relapse after remission of epilepsy)] and a prepared list of random allocations to break ties.

Whereas choice of drug was randomised, drug dosage and preparation were those used by the clinician in their everyday practice. The rate of titration, initial maintenance dose and any subsequent increments or decrements were decided by the clinician aided by guidelines (*Table 1*). The aim of treatment was to control seizures with a minimum effective dose of drug. This necessitated dosage increments if further seizures occurred, as is usual clinical practice.

The first patient was randomised in January 1999 and randomisation remained open until 31 August 2004. Patients were followed up at least until the end of the study (31 August 2005), with some patients contributing a small amount of follow-up after this date. The clinician and patient could during this time agree that withdrawal of the randomised drug was necessary because of intolerable side-effects, lack of efficacy or remission, or that an additional AED drug should be added because of lack of efficacy. The choice of additional or alternative drugs was determined by the clinician according to his/her view of optimal clinical practice.

TABLE I *Guidelines for initial maintenance doses and rates of titration*

Drug	Children aged <16 years (mg/kg/day)	Adults aged ⩾16 years (mg/dg)	Time to achieve maintenance dose (weeks)
Carbamazepine	15–20	600	4
Valproate	20–30	1000	2–3
Lamotrigine	3–6	150	6
Gabapentin	30–45	1200	1–2
Topiramate	3–6	150	6
Oxcarbazepine	15–30	900	3

Patients were to be seen for follow-up at 3, 6 and 12 months and at successive yearly intervals from the date of randomisation. If clinically indicated, more frequent follow-up was undertaken. At each visit, details of the occurrence of seizures and adverse events, hospital admissions and AED treatment were documented. For adverse effects, clinicians were asked to indicate whether they were clinically important. Where patients ceased to attend hospital clinics, follow-up was obtained from GPs or directly from the patient via a telephone interview.

There were two primary clinical outcome measures:

1. The time from randomisation to treatment failure [stopping the randomised drug due either to lack of efficacy (poor seizure control) or to intolerable side-effects, or both; or the addition of other AEDs, whichever was the earliest].
2. The time from randomisation to the achievement of a 1-year period of remission of seizures. Secondary clinical outcomes were the time from randomisation to a first seizure; time to achieve a 2-year remission; and the incidence of clinically important adverse events and side-effects emerging after randomisation. These were classified using a system described in Appendix 1.

The calculations of sample size were based on preliminary meta-analysis of individual patient data from VPS–CBZ studies.[42] We wished to establish that the lower 95% confidence limit (CL) for the old–new treatment comparisons exceeds –10% (non-inferiority), rather than establishing 'exact' equivalence within ±10%. With $\alpha = 0.05$ and $\beta = 10\%$, giving a 95% CL of ±10% around an overall response rate of 70% (1-year remission rates) and 70% (retention rate) at a median of 2.5 years of follow-up with power 90% ($\beta = 0.10$) required 445 patients per treatment group.

Assessment of QoL outcomes

The use of patient-based measures to enhance interpretation of clinical information has been strongly advocated[43,44] and patient-based QoL assessments are now commonplace in clinical trials. The Commission on Outcome Measurement in Epilepsy[45] has recommended that seizure frequency should represent only one element of a comprehensive assessment of outcome in clinical trials of epilepsy treatments, and that QoL represents another important measure.[45] Previous randomised studies comparing different drugs for epilepsy have either focused on clinical outcomes only or included only limited assessments of QoL. For example, Gillham and colleagues examined QoL in a 48-week study comparing LTG and CBZ[46] using the SEALS (Side Effects and Life Satisfaction) inventory, a 38-item questionnaire covering five QoL domains: worry, temper, cognition, dysphoria and tiredness. Overall, SEALS scores in the LTG group decreased significantly from baseline, with improvement across all five domains; patients taking CBZ experienced more short-term side-effects (first 4 weeks of treatment). The authors therefore concluded that LTG offers significant benefits over CBZ, in terms of greater tolerability and better health-related QoL. Meador and colleagues used a comprehensive neuropsychological battery which included cognitive, mood and QoL measures in a double-blind comparison of topiramate and valproate[47] and reported that TPM was associated with greater negative effects and slightly higher drop-out rates than was VPS. In a non-randomised study, Gilliam[48] has shown that in adult patients with established epilepsy attending a hospital outpatient clinic, adverse medication effects are strongly correlated with QoL.

In the SANAD (Standard and New Antiepileptic Drugs) trial, all patients meeting specified eligibility criteria were cued for QoL assessment. The criteria were aged 5 years and above and without any

TABLE 2 *Content of NEWQOL battery*

Physical domain	Psychological domain	Cognitive domain	Social domain
General health perception (single item; score of 0-4)	Hospital Anxiety and Depression Scale (HADS) (14-item scale; 7 items = anxiety; 7 items = depression; score of 0–21 for each domain)	Cognitive function [Aldenkamp Baker neuropsychological assessment schedule (ABNAS)] (24-item scale; score of 0–72)	Social activities (9-item scale; score of 0–27)
Health transition (single item; score of 0–4)	Sense of mastery (7-item scale; score of 0–21)		Social limitations (single item; score of 0–3)
Adverse Events Profile (AEP) (19-item scale; score of 0–57)	Seizure worry (2 items re. past/future seizures; score of 0–3)		Work limitations (5-item scale; score of 0–20)
	Felt stigma (3-item scale; score of 0–3)		

significant learning disability as judged by the randomising clinician from the history and examination. All eligible adults, defined as aged 16 years and above, were asked to self-complete QoL questionnaires at entry to SANAD and annually thereafter, up to a maximum of 4 years post-randomisation. Children aged 8–15 years were asked to self-complete QoL questionnaires at the same time points, and their parents were also asked to complete questionnaires to assess their perceptions of their child's QoL. For children aged 5–7 years, the QoL assessment was based on parental questionnaires only, also completed at baseline and annually thereafter. In addition, an abbreviated QoL assessment (parent-completed only for the children) was administered at 3 months after randomisation, to allow for detection of possible short-term impacts from taking AEDs.

Battery or profile QoL measures are acknowledged as appropriate in the context of clinical trials comparing the impact of alternative treatments,[49] since they provide detailed information across multiple components of QoL and so are more sensitive than summary or index measures for the detection of the range of, and any unexpected, effects. For both adults and children, the QoL assessment for SANAD involved the use of a battery of previously validated generic and epilepsy-specific measures. For adults, we used the NEWQOL (Newly Diagnosed Epilepsy Quality of Life) battery (*Table 2*), which was designed to examine physical, psychological, cognitive and social functioning in persons with new-onset seizures. All the measures included in NEWQOL have been extensively used and validated in previous studies by the Liverpool Epilepsy Research Group.[50] They were selected to reflect QoL domains identified as relevant and important to the target group for SANAD, that is, persons recently developing seizures, rather than – as is the case for many other epilepsy-specific measures – to those in whom epilepsy is established. In an independent validation exercise, NEWQOL has been shown to be valid, reliable and relevant to patients.[51] In addition, a revised 12-item version of the 'impact of epilepsy' (IoE) scale,[52] a single-item measure of global quality of life (GQoL)[53] and single items relating to education, employment and driving status were included in the adult assessment.

QoL assessment is a less well developed science in children than in adults and appropriate and well-validated measures are limited as a result. Historically, information about the QoL of children has been sought from their parents, acting as proxy informants, but there has been increasing recognition of the limits of proxy data and emphasis on the rights of children to speak for themselves. Recent research has indicated that despite potential cognitive and language difficulties in getting children, particularly very young children, to complete QoL assessments, both child and parent reports are valid.[54] In SANAD, the decision was made to employ child- and parent-based QoL measures in tandem. To this end, parents of all children recruited to SANAD and eligible for QoL assessment were asked to complete a proxy QoL assessment at baseline and annually thereafter, which comprised: the Rutter Child Behaviour Checklist (CBC),[55] the Adverse Events Profile (AEP),[56] the 'general health perceptions' subscale of the Child Health Questionnaire (CHQ),[57] a single-item measure of GQoL[53] and

TABLE 3 *Summary of QoL assessments*

	Adults	Children aged 5–7 years	Children aged 8–11 years	Children aged 12–15 years
Baseline	NEWQOL; IoE; GQoL	Parent-completed: CBC; CHQ; AEP; GQoL	Self-completed: KINDL, EI, AE Parent-completed: CBC; GHP; AEP, GQoL	Self-completed: KINDL, EI, AE Parent-completed: CBC; GHP; AEP, GQoL
3 months	HADS, AEP	Parent-completed: AEP	Parent-completed: AEP	Parent-completed: AEP
1 year	NEWQOL; IoE; GQoL	Parent-completed: CBC; CHQ; AEP; GQoL	Self-completed: KINDL, AE Parent-completed: CBC; GHP; AEP, GQoL	Self-completed: KINDL, EI, AE Parent-completed: CBC; GHP; AEP, GQoL
2 years	NEWQOL; IoE; GQoL	Parent-completed: CBC; CHQ; AEP; GQoL	Self-completed: KINDL, AE Parent-completed: CBC; GHP; AEP, GQoL	Self-completed: KINDL, EI, AE Parent-completed: CBC; GHP; AEP, GQoL
3 years	NEWQOL; IoE; GQoL	Parent-completed: CBC; CHQ; AEP; GQoL	Self-completed: KINDL, AE Parent-completed: CBC; GHP; AEP, GQoL	Self-completed: KINDL, EI, AE Parent-completed: CBC; GHP; AEP, GQoL
4 years	NEWQOL; IoE; GQoL	Parent-completed: CBC; CHQ; AEP; GQoL	Self-completed: KINDL, AE Parent-completed: CBC; GHP; AEP, GQoL	Self-completed: KINDL, EI, AE Parent-completed: CBC; GHP; AEP, GQoL

single items relating to school attendance and progress. Children aged 8–15 years completed a 40-item generic health status measure, the KINDL Questionnaire, which assesses functioning across four QoL domains: physical, social, emotional and functional (www.KINDL.org). KINDL has been validated for use in children across this age range[58] and shown to have good psychometric properties. However, since its authors recommend that it be supplemented by disease-specific modules, older children (12–15 years) also completed the 12-item 'epilepsy impact' (EI) and the four-item 'attitude to epilepsy' (AE) subscales of the Quality of Life in Epilepsy Inventory for Adolescents (QOLIE-AD),[59] and younger children (8–11 years) completed the four-item AE subscale only. A summary of the QoL assessments is given in *Table 3*. Copies of all questionnaires are available, on request, from the authors.

The QoL questionnaires were administered as early as possible following randomisation and then at 3 months and yearly from the date of randomisation. Questionnaires were sent by post, with a single mailed reminder being sent to non-responders 3 weeks after the initial mailing and telephone contact after a further 3-week period to those failing to respond to the mailed reminder. All questionnaires were accompanied by a cover letter, explaining the purpose of the QoL study (see Appendix 2) and a reply-paid envelope. As a methodological addition to the study (see Appendix 2), the wording of the cover letter was varied to include or exclude reference to the length of time estimated to be required to complete the questionnaire. For children, parents received, along with their own questionnaire, a form for consenting to their child taking part in the QoL study; they were asked to complete and return this form to the study office, indicating reasons for refusal to consent where they did so. Where they agreed, they were asked to hand on to their child the relevant questionnaire and accompanying cover letter. A blank envelope was supplied so that children could, should they so desire, return their completed questionnaire confidentially, even though in the same pre-paid envelope as their parents. All patients and parents were supplied with change of address cards at each contact, and asked to notify the study office of any change in their home address. Patients or parents declining to return either a baseline or 3-month questionnaire were sent no further follow-up questionnaires, the assumption being that those who declined to complete questionnaires at this early stage in the life of trial were 'active' refusers who would be unlikely to do so later [this assumption rested on the finding, in our earlier trial of management of single or few seizures, that patients failing to respond to the QoL assessment

at baseline also failed to respond to subsequent follow-up (A Jacoby, unpublished data)]. However, all patients completing **either** the baseline **or** the 3-month assessment were then cued to receive questionnaires at **all** subsequent time points, regardless of whether or not they returned them at each time point, thus maximising the amount of data available for analysis.

Assessment of health economic outcomes

The aim of the economic evaluation in SANAD was to assess the cost-effectiveness of the new AEDs relative to the standard AEDs. Separate evaluations were performed for Arm A (where the current first-line treatment, CBZ, was compared against GBP, LTG, OXC and TPM) and Arm B (where the current first-line treatment, VPS, was compared against LTG and TPM). The perspective adopted for the analyses was that of the NHS and social services. The period for the analysis was 2 years from randomisation.

Assessment of costs

Patients' use of resources can be categorised under three general headings: (1) consumption of AEDs; (2) resource use associated with the management of adverse events requiring hospitalisation; and (3) other healthcare and social services resource use.

With respect to AEDs, data were collected in the clinical forms for all patients regarding which AEDs they were taking, what doses they were taking and how long they were taking each AED dose. Application of unit cost data from the BNF[60] allowed estimates to be made of the total AED cost per patient over a 2-year period. AED costs in year 2 were discounted at the UK Treasury recommended rate of 3.5%. All AED costs are at 2005 prices.

For CBZ, LTG and VPS, a range of both proprietary and non-proprietary drugs are available at varying costs. To allow for the possible impact of high and low drug costs on the economic evaluation, separate analyses were performed using the most expensive and cheapest costs for each drug. Specifically, in Arm A separate analyses were run for CBZ_{low} and LTG_{low}, CBZ_{low} and LTG_{high}, CBZ_{high} and LTG_{low} and CBZ_{high} and LTG_{high}. In Arm B, separate analyses were run for the same combinations of VPS_{low}, VPS_{high}, LTG_{low} and LTG_{high}.

With respect to adverse events, data were collected in the clinical forms on each patient experiencing an adverse event requiring hospitalisation. For each event, the hospital specialty was recorded, with a distinction being made between outpatient attendances and events requiring an inpatient stay. Unit cost data were obtained from the TFR2A and TFR2B specialty and programme costs returns to the Department of Health by Trusts for the year ending 31 March 2004. These costs were inflated to 2005 prices through the application of the Hospital and Community Health Services (HCHS) Pay and Prices Index. Additional unit cost data were obtained from Curtis and Netten.[61] As with the AED costs, year 2 costs were discounted at 3.5%, and all costs are at 2005 prices.

Data on other healthcare and social services resource use were obtained from patient responses to specific resource use questions included in the QoL questionnaires. These included questions on GP contacts, nurse contacts, other health professional contacts, social services contacts, use of the ambulance service and any tests or investigations the patients may have had. Unit cost data were obtained from Curtis and Netten[61] and from the Finance Department of Walton NHS Hospital Trust. Again, costs in year 2 were discounted at 3.5%, with all costs being reported at 2005 prices.

In all cases, patients were asked to report resource use for the 3-month period prior to completing the questionnaire. As indicated above, the QoL questionnaires were administered at 3 months, and 1, 2, 3 and 4 years. The analyses presented in this report are for data collected at 2 years. This means that patient-reported resource use data were comprehensive for months 1–3, but that extrapolations had to be made for months 4–9 and for months 13–21. To estimate year 1 costs, the costs in months 10–12 were multiplied by three and added to the costs for months 1–3. Year 2 costs were estimated by multiplying the cost in months 22–24 by four.

A breakdown of the individual items of resource use and the corresponding unit cost applied to each item is reported in *Table 4*. The table includes resource use associated with the management of adverse events requiring hospitalisation and other healthcare and social services resources, but does not include a breakdown of the AED costs. The reason for this is that it is not practical to attempt to summarise unit cost data for drug use due to the large variation in drug dosage and time on particular

TABLE 4 *Breakdown of resource use and corresponding unit cost data*

Resource	Unit cost (£) (2005 prices)	Source of unit cost data
Adverse events requiring hospitalisation		
Intensive care unit	1378 per day	Ref. 61
Psychiatric ward inpatient	206 per day	Ref. 61
Psychiatric ward outpatient	154 per contact	Ref. 61
Medical ward inpatient	310 per day	Ref. 61
Medical ward outpatient	93 per contact	Ref. 61
Surgical ward inpatient	416 per day	TFR[b]
Surgical ward outpatient	108 per contact	TFR[b]
Short-stay A&E observation	352 per day	Ref. 61
A&E outpatient	110 per contact	Ref. 61
Other	Range of values[a]	Ref. 61/TFR[b]
Other		
Nurse at GP surgery	10 per consultation	Ref. 61
GP at surgery	24 per consultation	Ref. 61
Nurse at home	17 per visit	Ref. 61
GP at home	69 per visit	Ref. 61
Ambulance	199 per journey[c]	Ref. 61
Blood test	5 per test	FDW[d]
Urine test	2 per test	FDW[d]
Ultrasound	92 per scan	FDW[d]
X-ray	16 per test	FDW[d]
Computer tomography scan	49 per scan	FDW[d]
Magnetic resonance imaging scan	224 per scan	FDW[d]
EEG	149 per scan	FDW[d]
Health visitor	76 per contact[e]	Ref. 61
Social worker	106 per contact[e]	Ref. 61
Disablement resettlement officer	53 per contact[e]	Ref. 61
Psychologist	72 per contact[e]	Ref. 61
Counsellor	36 per contact[e]	Ref. 61
Educational/vocational officer	28 per contact[e]	Ref. 61

[a] 37 other contacts were reported and costed.
[b] TFR2A and TFR2B specialty and programme costs returns to the Department of Health by Trusts.
[c] Average of unit costs of paramedic unit, emergency ambulance and patient transport service.
[d] Finance Department of Walton NHS Hospital Trust.
[e] Assumes 1 hour per contact.

drugs among patients. As indicated above, unit cost data for the AEDs are taken from the BNF for 2005.

Assessment of outcome

Patient outcome for the economic evaluation was assessed in two ways: (1) the estimation of the number of quality-adjusted life-years (QALYs) enjoyed by patients (adults only); and (2) the numbers of seizures experienced by patients (adults and children combined).

Estimation of QALYs was made possible by the inclusion of the EuroQoL EQ-5D questionnaire in the QoL questionnaires administered at baseline, 1 year and 2 years.[62] The estimation of QALYs for children was not possible because EQ-5D data were not collected from children. Having elicited patients' current health status according to the five dimensions of the EQ-5D, UK tariff values representing QoL weights were applied to the health states. QALYs were estimated using an area under the curve (AUC) approach. To illustrate this approach, consider an individual whose baseline and 1-year QoL weights are 0.6 and 0.8, respectively. When located on a two-dimensional plane where the y-axis corresponds to the QoL weight and the x-axis corresponds to time in years, the area under the curve joining these two points together defines a trapezium, the area of which is equal to the number of QALYs enjoyed by the patient in year 1. The area of a trapezium with a base width of 1 year and whose sides are defined as x and y is equal to $\frac{1}{2}(x + y)$. In this example, $x = 0.6$ and $y = 0.8$. Hence the AUC corresponds to 0.7 QALYs.

The above approach was used to estimate the number of QALYs enjoyed by each patient separately in years 1 and 2. The year 2 QALYs were then discounted at 3.5% before being added to the year 1 QALYs to give an estimate of the total number of QALYs enjoyed by each patient over the 2-year analysis period. The average number of QALYs enjoyed by patients in each drug group was then estimated.

The number of seizures experienced by each patient was recorded in the clinical forms. The total number of seizures attributable to each patient (adults and children) was calculated by adding the number of seizures experienced in year 1 to the discounted (at 3.5%) number of seizures experienced in year two. The average number of seizures experienced by patients in each drug group was then estimated.

The AUC approach described above implicitly assumes that the benefit of any health improvement occurs at the mid-points of years 1 and 2, thus giving rise to a linear interpolation between EQ-5D tariff values at baseline and year 1, and between values at year 1 and year 2. This is the method most commonly employed in AUC analyses reported in the literature.[63] However, many other assumptions could be made, each of which may have an impact on the results. In the absence of any *a priori* evidence suggesting that one particular relationship is more appropriate than any other, the effect of assuming extreme values was explored. Specifically, the estimation of QALYs was redone assuming (i) that the benefit of any health improvement occurs at the beginning of years 1 and 2 and (ii) that the benefit of any health improvement occurs at the end of years 1 and 2. These two assumptions give rise to 'stepped' curves. The impact of these two alternative assumptions on the relative cost-effectiveness of the AEDs was investigated.

Assessment of cost-effectiveness

In order to assess the relative cost-effectiveness of the AEDs, data on costs and outcome were brought together to estimate cost-effectiveness ratios. The AEDs were compared in terms of two distinct cost-effectiveness ratios, cost per QALY gained and cost per seizure avoided.

Considering first the cost per QALY analysis, data are available on the total cost attributable to each patient over 2 years and the total number of QALYs enjoyed by patients during that period. For each group of patients defined by the drug to which they were initially randomised, an average cost per patient and an average number of QALYs enjoyed by each patient can be estimated. An incremental analysis can then be performed in which the AEDs are compared in terms of the extra costs attributable to one drug compared with another in order to generate one extra QALY. Taking Arm A as an example with CBZ as the initial comparator, the AED with the next highest average cost is selected and the incremental cost of the new AED relative to CBZ is estimated (that is, the extra cost of the new AED over and above the cost of CBZ). The incremental QALY gain is also estimated. Dividing the incremental cost by the incremental QALY gain defines the incremental cost-effectiveness ratio (ICER) for the new AED relative to CBZ. The ICER indicates the extra cost that needs to be incurred to generate one extra QALY. This process is repeated for the next most expensive AED, allowing an ICER for this drug to be calculated relative to the previous AED. This process is repeated for the remaining drugs in Arm A. ICERs in Arm B are calculated in the same way, with VPS being the initial comparator.

A similar analysis can be performed to estimate cost per seizure avoided. For each drug group, an average cost per patient and average number of seizures experienced are calculated. Taking CBZ and VPS as baseline comparators, ICERs in the form of incremental cost per seizure avoided can then be estimated for those AEDs which cost more but which result in fewer seizures. AEDs which cost more and result in more seizures will be dominated (see the next section).

The cost-effectiveness plane

The ICERs for the new AEDs represent point estimates of the relative efficiency of the drugs and can be located on the cost-effectiveness plane (*Figure 1*). The cost-effectiveness plane is a two-dimensional space in which the origin represents the comparator drugs (CBZ or VPS). The *x*-axis represents the average difference in effectiveness per patient between the comparator drugs and the new AEDs, and the *y*-axis represents the average difference in cost per patient between the drugs. The four quadrants are conventionally referred to as points on the compass, namely north-west (NW), north-east (NE), south-west (SW) and south-east (SE). The ICERs can be plotted as points on this plane, with the slope of the line from the origin to the ICER representing the value of the ICER. Treatments with ICERs located in the NW quadrant (more costly, less effective) are said to be dominated by the comparator treatment, whereas

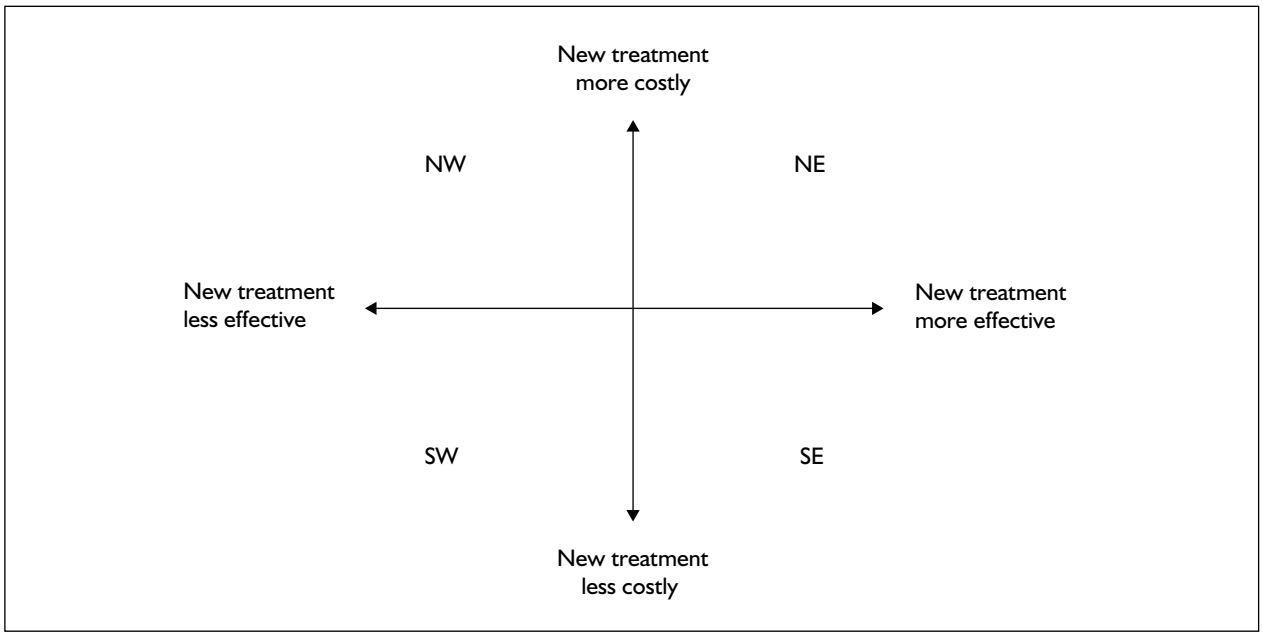


FIGURE 1 *The cost-effectiveness plane*

treatments with ICERs located in the SE quadrant (less costly, more effective) are said to dominate the comparator treatment. In practice, most new treatments locate in the NE quadrant where increased effectiveness is achieved at increased cost. In this instance (and in the case of the SW quadrant where treatments are less costly and less effective), the decision to adopt the new treatment will depend on whether the ICER lies below the acceptable ceiling ratio of the decision-maker. If the decision-maker's willingness to pay for a unit of effectiveness (λ) is greater than the ICER, then on efficiency grounds the treatment should be recommended for adoption.

Allowing for uncertainty

The point estimates of the ICERs are subject to uncertainty and it is therefore important that this uncertainty is taken into account. Because of the problems associated with estimating confidence intervals (CIs) for ratio statistics, the approach of non-parametric bootstrapping is adopted to represent the uncertainty surrounding the ICER estimates.[64] Cost-effectiveness acceptability curves (CEACs), which summarise the evidence in support of the new AEDs being cost-effective for all potential values of λ, are also estimated. The probabilistic interpretation of these curves should be from a Bayesian perspective. In effect, the CEAC provides information to decision-makers on the level of uncertainty associated with a potential decision to recommend a new AED. For example, a 0.82 probability of a drug being cost-effective at a ceiling ratio of £30,000 per QALY, say, implies an error probability (i.e. the probability of making a wrong decision) of 0.18 (1 – 0.82). In making a decision regarding the potential recommendation of a new drug, the decision-maker must weigh up these probabilities against one another. Alternatively, instead of deciding whether or not to recommend the new drug on the basis of the currently available evidence, the decision-maker may demand an expected value of perfect information (EVPI) analysis to compare the expected cost of the uncertainty with the value of conducting further research to reduce the uncertainty (see Claxton and colleagues[65] for more details on EVPI analysis).

Sensitivity analysis on the method employed to estimate QALYs (the AUC approach) is also undertaken as detailed above.

The introduction of oxcarbazepine

Because OXC was added to Arm A only after the trial had been running for some time (OXC was introduced on 1 June 2001), two separate analyses are presented for Arm A: (1) a comparison of OXC with GBP, LTG, CBZ and TPM using patient data collected after 1 June 2001; and (2) a comparison of CBZ with GBP, LTG and TPM using patient data from the entire trial period.

Assessment of clinical outcomes

The statistical analysis plan for clinical outcomes, as approved by the Trial Steering Group and Data Monitoring and Ethics Committee, is presented in

Appendix 3. Most importantly, it was planned to undertake both an intention-to-treat (ITT) analysis and a per-protocol (PP) analysis of clinical outcomes. ITT analysis would be most conservative for tests of differences between drugs, but PP analysis would be most conservative when considering issues of equivalence. These respective populations are described in detail in Appendix 3 and in the flow charts of patients' disposition (see Chapter 3). For the PP analyses, the clinical and statistical issues of informative censoring have been identified. The problem arises for the remission outcomes as follows: if treatment failures prior to achievement of a period of remission are censored at the date of treatment failure, the log-rank analysis assumes that time to achieve a remission for an individual is independent of any mechanism which causes that individual's time to be censored at some time. The log-rank analysis would therefore seem inappropriate as patients with a poor prognosis of remission would more likely be withdrawn from a drug for inadequate seizure control, leading to selection bias in the analysis. For this reason, the log-rank analysis censoring treatment failures before a 12-month remission is not considered appropriate here and the cumulative incidence analysis is preferred; however the *p*-values from the log-rank analysis are presented for consistency. The most appropriate method of analysis of causal effects of AEDs on 12-month remission is an area of ongoing research by our group.

The Trial Management Group suggested that a number of additional analyses of clinical outcomes be undertaken to take account of important clinical issues. These additional analyses were requested before sight of any results. The most important of these changes were to conduct analyses excluding patients diagnosed during follow-up as not having epilepsy (as these patients could not contribute to the final primary outcomes in a meaningful way), and to censor time to first seizure at the point at which AED was withdrawn because of a period of remission. Clinical members also requested subgroup analyses based on groups of patients definitely diagnosed as having partial epilepsy (Arm A) or generalised epilepsy (Arm B). Because of methodological work undertaken by members of the Trial Management Group, competing risks analyses were undertaken for the time to treatment failure outcome. Finally, analyses were undertaken to examine whether there were systematic differences in outcomes between patients randomised before 1 June 2001 and patents randomised after this date (on which OXC was added to randomisation within Arm A).

Ninety centres recruited patients, as summarised in *Table 5*, where centres are listed in order of numbers of patients recruited.

A full list of collaborators is provided in Appendix 4.

As a check on eligibility, 'Dates of most recent seizures' and 'Number of seizures ever' were examined to make sure that patients had experienced at least two seizures within the year prior to randomisation; 2414/2437 patients were confirmed as meeting this criterion. The interval between the most recent seizure and

TABLE 5 *Numbers randomised at recruiting centres*

Centre code	Hospital	Number randomised		
		Arm A	Arm B	Total
001	Walton Centre for Neurology and Neurosurgery, Liverpool	426	91	517
138	Wrexham Maelor Hospital, Wrexham	188	50	238
070	University Hospital of Wales, Cardiff	122	50	172
141	Royal Bolton Hospital, Bolton	102	18	120
051	Dundee Royal Infirmary, Dundee	64	24	88
095	Royal Victoria Infirmary, Newcastle upon Tyne	51	36	87
012	Doncaster Royal Infirmary, Doncaster	63	22	85
031	Glan Clwyd Hospital, Bodelwyddan	69	10	79
112	Sunderland District General Hospital, Sunderland	32	39	71
192	Whiston Hospital, Prescot	27	44	71
011	Alder Hey Children's Hospital, Liverpool	27	39	66
025	St James's University Hospital, Leeds	48	17	65
092	Royal Hallamshire Hospital, Sheffield	40	12	52
	11 Hospitals recruited 20–39 patients	202	106	308
	15 Hospitals recruited 10–19 patients	127	73	200
	51 Hospitals recruited 1–9 patients	133	85	218

randomisation was greater than 1 year for 14 patients, five patients were recorded as having only one seizure and for four patients there were no data on number or dates of seizures prior to randomisation. Patients not confirmed as meeting eligibility criteria are included in analyses by ITT. All patients were aged 5 years or over.

A small number of randomisation errors occurred. Four patients were incorrectly randomised to the wrong arm by the recruiting clinician. As soon as the mistake was recognised, the patients were re-randomised to the correct arm. Sixteen patients were randomised with an incorrect treatment history specified by the clinician. These patients were not re-randomised and the original details remain unchanged on the database. One patient was mistakenly randomised twice, on two separate occasions (TPM allocated drug on both occasions coincidentally). Details from the second randomisation were deleted.

Chapter 3

Results

Arm A: carbamazepine as standard drug

The first patient was randomised into the study on 12 January 1999 and randomisation continued up to 31 August 2004. Attempts were made to follow up all patients to, at the latest, a point in time between 1 May 2005 and 31 August 2005, although some follow-up data were collected up to 13 January 2006. In total, 1721 patients were randomised (*Table 6*).

The numbers randomised to CBZ, GBP, LTG and TPM are balanced across minimisation factors (centre, sex and clinical history) for the recruitment period 12 January 1999 to 31 February 2001, as are the numbers randomised to CBZ, GBP, LTG, TPM, OXC for the recruitment period 1 June 2001 to 31 August 2004.

TABLE 6 *Number of patients randomised in Arm A*

Drug	No. randomised (%)
CBZ	378 (22)
GBP	377 (22)
LTG	378 (22)
OXC	210 (12)
TPM	378 (22)
Total	1721

During the course of the study, a number of patients in Arm A were lost to follow-up. The reasons and the relationship of any deaths to epilepsy are given in *Tables 7* and *8*.

It should be noted that epilepsy-related deaths (defined to include accidental deaths caused by seizures, status epilepticus and all sudden deaths) were rare in the study and too infrequent to allow any examination of differential risks between drugs. Other deaths were more commonly seen in Arm A than in Arm B due to the older patients recruited into this arm of the study (*Figure 2*).

A summary of baseline patient characteristics is given in *Table 9*, which shows that randomisation provided well-balanced treatment groups.

As expected, the majority of those randomised within Arm A were diagnosed as having a partial epilepsy, with only 10% being unclassified. Thus Arm A fulfilled the expectation that it would be a pragmatic study of drugs with a spectrum of activity largely restricted to partial seizures with or without secondary generalisation.

A flow chart of patient disposition and numbers contributing to ITT and PP populations is presented in *Figure 3*.

TABLE 7 *Withdrawals [n (%)] from further follow-up (withdrawals from study) for Arm A*

Reason for withdrawal from study	CBZ (*n* = 378)	GBP (*n* = 377)	LTG (*n* = 378)	OXC (*n* = 210)	TPM (*n* = 378)	Total (*n* = 1721)
Consent withdrawn	7 (1.9)	8 (2.1)	8 (2.1)	5 (2.4)	10 (2.6)	38 (2.2)
Not epilepsy	10 (2.6)	10 (2.7)	8 (2.1)	8 (3.8)	8 (2.1)	44 (2.6)
Other reasons[a]	1 (0.3)	0	0	0	0	1 (0.1)

[a] Returned to live abroad.

TABLE 8 *Summary of deaths by treatment group for Arm A*

Deaths	CBZ (*n* = 378)	GBP (*n* = 377)	LTG (*n* = 378)	OXC (*n* = 210)	TPM (*n* = 378)	Total (*n* = 1721)
Epilepsy related	1	2	4	3	0	10
Non-epilepsy related	17	17	8	2	17	61
Total, *n* (%)	18 (4.8)	19 (5.0)	12 (3.2)	5 (2.4)	17 (4.5)	71 (4.1)

TABLE 9 *Baseline demographic and clinical characteristics for Arm A*

	CBZ (*n* = 378)	GBP (*n* = 377)	LTG (*n* = 378)	OXC (*n* = 210)	TPM (*n* = 378)	Total (*n* = 1721)
Sex, *n* (%)						
Male	208 (55)	207 (55)	208 (55)	111 (53)	208 (55)	942 (55)
Female	170 (45)	170 (45)	170 (45)	99 (47)	170 (45)	779 (45)
Treatment history, *n* (%)						
Untreated	309 (81.8)	306 (81.2)	308 (81.5)	181 (86.2)	308 (81.5)	1412 (82.1)
Monotherapy (not optimally treated)	60 (15.9)	60 (15.9)	61 (16.1)	25 (11.9)	60 (15.9)	266 (15.5)
Recent seizures after remission	9 (2.4)	11 (2.9)	9 (2.4)	4 (1.9)	10 (2.7)	43 (2.5)
History, *n* (%)						
Learning disability	20 (5.3)	17 (4.5)	23 (6.1)	4 (1.9)	21 (5.6)	85 (4.9)
Neurological deficit	34 (9.0)	28 (7.4)	32 (8.5)	15 (7.1)	30 (7.9)	139 (8.1)
Neurological disorder, *n* (%)						
Stroke/cerebrovascular	32 (8.5)	27 (7.2)	20 (5.3)	10 (4.8)	19 (5.0)	108 (6.3)
Intracranial surgery	13 (3.4)	17 (4.5)	15 (4.0)	2 (1.0)	24 (6.4)	71 (4.1)
Head injury	12 (3.2)	17 (4.5)	18 (4.8)	10 (4.8)	26 (6.9)	83 (4.8)
Meningitis/encephalitis	4 (1.1)	7 (1.9)	12 (3.2)	3 (1.4)	8 (2.1)	34 (2.0)
Other	28 (7.4)	24 (6.4)	29 (7.7)	11 (5.2)	32 (8.5)	124 (7.2)
History of seizures, *n* (%)						
Febrile convulsions	27 (7.1)	16 (4.2)	25 (6.6)	7 (3.3)	17 (4.5)	92 (5.4)
Any other acute symptomatic seizures	6 (1.6)	15 (4.0)	18 (4.8)	8 (3.8)	13 (3.4)	60 (3.5)
Epilepsy in relatives first-degree	39 (10.3)	44 (11.7)	38 (10.1)	24 (11.4)	34 (9.0)	179 (10.0)
Epilepsy syndrome, *n* (%)[a]						
Idiopathic partial	4 (1.1)	5 (1.3)	6 (1.6)	3 (1.4)	6 (1.6)	24 (1.4)
Symptomatic or cryptogenic partial	338 (89.4)	333 (88.6)	330 (88.0)	180 (85.7)	322 (85.4)	1503 (87.6)
Idiopathic generalised	3 (0.8)	3 (0.8)	4 (1.1)	5 (2.4)	7 (1.9)	22 (1.3)
Other syndrome	2 (0.5)	0 (0)	0 (0)	1 (0.5)	1 (0.3)	4 (0.2)
Unclassified	31 (8.2)	35 (9.3)	35 (9.3)	21 (10.0)	41 (10.9)	163 (9.5)
Median interval between 1st and most recent seizure (25th, 75th centile), days[b]	465 (162, 1720)	446 (156, 2195)	492 (165, 1765)	463 (155, 1470)	488 (153, 1949)	467 (156, 1889)
Median interval between most recent seizure and randomisation (25th, 75th centile), days[c]	13 (4, 37)	13 (3, 37)	14 (3, 38)	14 (4, 41)	12 (3, 33)	13 (3, 37)
Median number of seizures (25th, 75th centile)[d]	12 (4, 65)	12 (4, 70)	12 (4, 60)	11 (4, 51)	12 (4, 80)	12 (4, 63)
Mean age ± SD (years)	39.2 ± 18.3	37.8 ± 17.9	36.8 ± 18.3	40.1 ± 18.0	38.4 ± 18.6	38.3 ± 18.3

[a] Missing data for epilepsy syndrome for 1 individual on GBP, 3 individuals on LTG and 1 individual on TPM.
[b] Missing dates of seizures for 1 individual on TPM.
[c] Missing data for dates of seizures for 1 individual on TPM.
[d] Missing number of seizures for 1 individual on TPM.

Arm A achieved a relatively complete follow-up. When the 83 patients withdrawn from study and 71 patients who died are excluded from the following calculations, and follow-up data received after 31 August 2005 are truncated at 31 August 2005, overall, 5406 years of follow-up were achieved compared with 5762 years that could be expected. The overall proportion of follow-up achieved is therefore 94% (*Table 10*).

One of the two primary outcomes for the study was time to the failure of the randomised drug as judged by its withdrawal or the addition of another AED. The number of patients

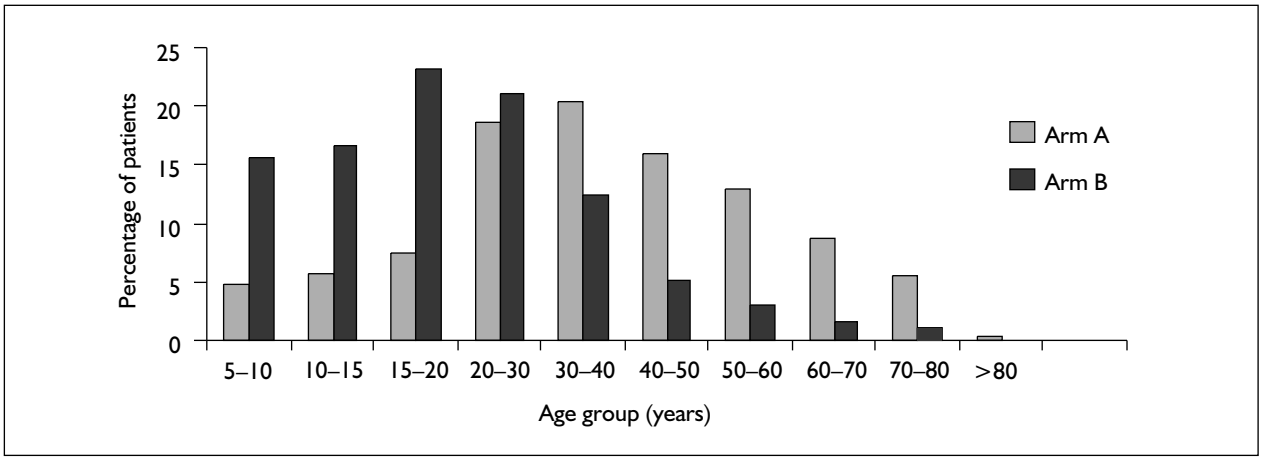


FIGURE 2 *Age at randomisation, Arms A and B*

TABLE 10 *Completeness of follow-up for Arm A*

Follow-up (years)	CBZ (*n* = 342)	GBP (*n* = 340)	LTG (*n* = 350)	OXC (*n* = 192)	TPM (*n* = 343)	Total (*n* = 1567)
Actual	1227	1195	1276	488	1220	5406
Expected	1296	1284	1350	525	1307	5762
Actual/expected (%)	95	93	95	93	93	94
Median (min., max.)	3.6 (0.7, 6.6)	3.5 (0, 6.4)	3.7 (0.8, 6.5)	2.7 (0.5, 4.1)	3.6 (0, 6.5)	3.4 (0, 6.6)

withdrawing from the randomised drug and/or having new AED added and/or withdrawing from study are presented in *Table 11*. The reason for drug withdrawal or addition or study withdrawal is defined as the earliest event for the purposes of these tables.

The timing of the different treatment failure events was explored using a frequency plot (*Figure 4*). This shows that withdrawal for unacceptable side-effects is largely limited to the early post-randomisation period, whereas the timing of withdrawal for inadequate seizure control (ISC) [with or without unacceptable adverse events (UAEs)] occurs much later, because of the necessity for upward titration of dose required before withdrawal for inadequate seizure control can occur. To allow for possible dependence between the different withdrawal risks, cumulative incidence analyses are presented, the analysis for which does not assume that censoring is non-informative.

Because of the pragmatic nature of the trial design and the absence of blinding it is important to assess the doses of drugs used and consider the degree to which the full dose ranges were explored before treatment failure events. These data are presented in *Tables 12* and *13*.

There is satisfactory evidence that clinicians did explore a full dosing range before accepting treatment failure because of ISC. As would be expected, doses associated with UAEs were consistently lower than those associated with ISC. Patients achieving remission tended to do so on low doses of randomised drug.

Examination of data for oxcarbazepine

The interpretation of the results from Arm A of the study is complicated by the inclusion of OXC in June 2001. Because of this, the most conservative analysis of the comparative effectiveness of OXC will include a smaller number of patients randomised after this date, with consequent loss of power. Some sensitivity analysis has been undertaken to determine whether valid comparison can be made between OXC patients and the patients randomised to other drugs throughout the entirety of the study. To do this, times to treatment failure and 12-month remission (the two primary outcomes) were compared for patients randomised pre- and post-June 2001 (excluding OXC patients). There were some differences in outcomes between the two recruitment periods divided by 1 June 2001, with a trend towards greater hazard for treatment failure later in the study but also for an increased likelihood of achieving a 12-month remission of

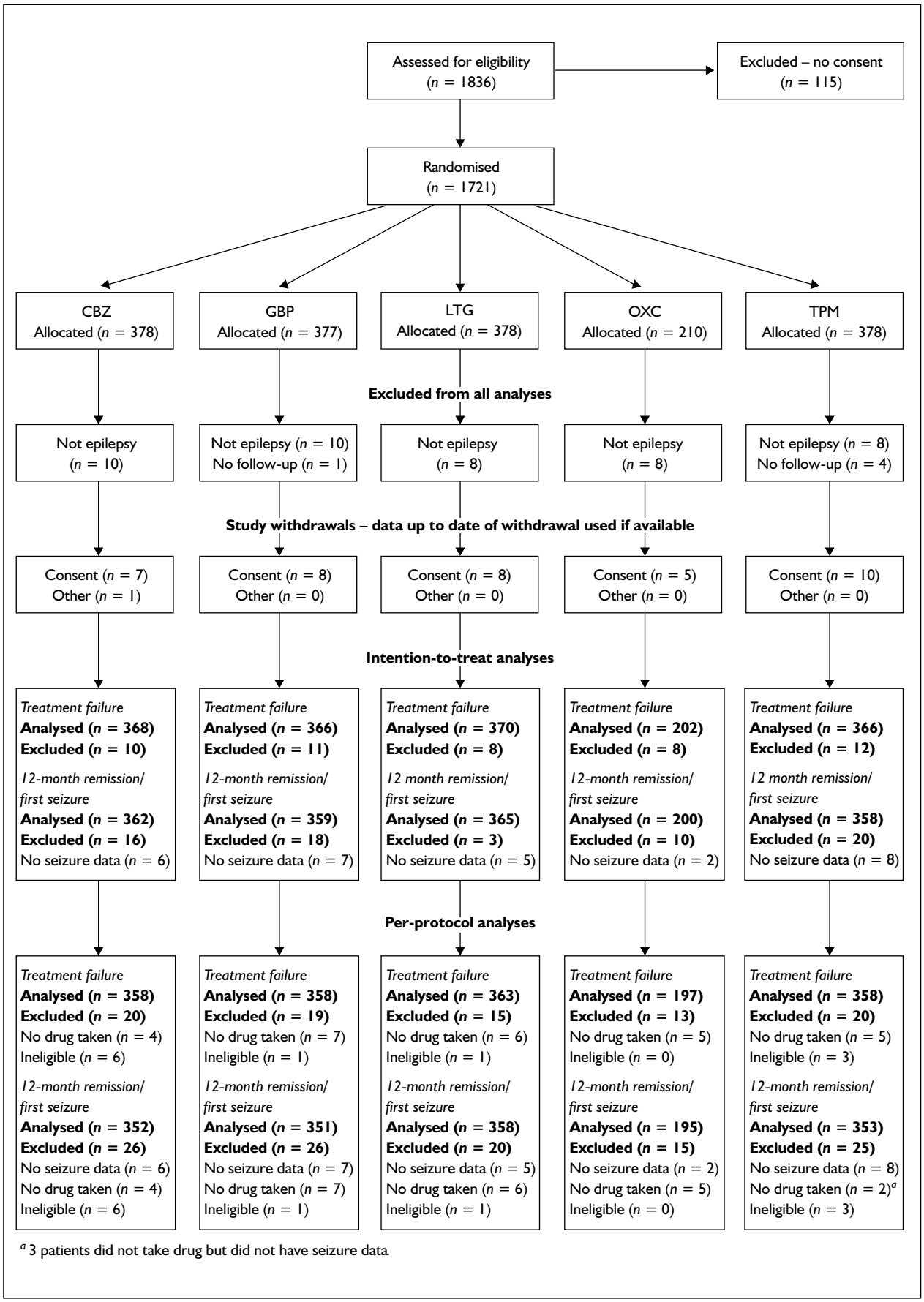


FIGURE 3 *Patient disposition for Arm A*

TABLE 11 *Reasons for treatment termination for Arm A: entries are number of patients with percentages in parentheses*

Reason for termination	CBZ (*n* = 378)	GBP(1) (*n* = 376)	LTG (*n* = 378)	OXC (*n* = 210)	TPM[a] (*n* = 374)	Total (*n* = 1716)
Treatment failure[b]						
Inadequate seizure control (ISC)	43 (11.4)	99 (26.3)	60 (15.9)	24 (11.4)	55 (14.7)	281 (16.4)
Unacceptable adverse events (UAE)	102 (27.0)	57 (15.2)	60 (15.9)	49 (23.3)	101 (27.0)	369 (21.5)
ISC and UAE[c]	20 (5.3)	32 (8.5)	11 (2.9)	11 (5.2)	28 (7.5)	102 (5.9)
Non-compliance	2 (0.5)	1 (0.3)	1 (0.3)	2 (1.0)	0 (0)	6 (0.3)
Epilepsy-related death	0 (0)	1 (0.3)	2 (0.5)	1 (0.5)	0 (0)	4 (0.2)
Perceived adverse event	2 (0.5)	3 (0.8)	1 (0.3)	1 (0.5)	2 (0.5)	9 (0.5)
Pregnancy	0 (0)	1 (0.3)	2 (0.5)	1 (0.5)	3 (0.8)	7 (0.4)
Patient decision	1 (0.3)	1 (0.3)	2 (0.5)	1 (0.5)	4 (1.1)	9 (0.5)
Perceived remission[d]	7 (1.9)	14 (3.7)	16 (4.2)	2 (1.0)	9 (2.4)	48 (2.8)
Total number of treatment failures	**177 (47)**	**209 (56)**	**155 (41)**	**92 (44)**	**202 (54)**	**835 (49)**
Non-treatment failure[e]						
Consent withdrawn	6 (1.6)	3 (0.8)	6 (1.6)	1 (0.5)	8 (2.1)	24 (1.4)
Non-epilepsy-related death	10 (2.6)	9 (2.4)	5 (1.3)	1 (0.5)	8 (2.1)	33 (1.9)
Lost to follow-up	0 (0)	0 (0)	0 (0)	1 (0.5)	0 (0)	1 (0.1)
Not epilepsy	6 (1.6)	2 (0.5)	4 (1.1)	6 (2.9)	4 (1.1)	22 (1.3)
Other	3 (0.8)	5 (1.3)	4 (1.1)	4 (1.9)	0 (0)	16 (0.9)
Remission of epilepsy	25 (6.6)	21 (5.6)	23 (6.1)	12 (5.7)	19 (5.1)	100 (5.8)
Total number of non-treatment failure withdrawals	**50 (13)**	**40 (11)**	**42 (11)**	**25 (12)**	**39 (10)**	**196 (11.4)**
Still on drug at end of study	**151 (40)**	**127 (34)**	**181 (48)**	**93 (44)**	**133 (36)**	**685 (40)**

[a] No follow-up data for 1 individual on GBP and 4 individuals on TPM.
[b] Withdrawn from randomised drug/study/other drug added for bad reason and counted as event in time to treatment failure analysis.
[c] Treated as ISC in competing risks analyses.
[d] Period in remission is less than 12 months.
[e] Censored at date of termination in time to treatment failure analysis.

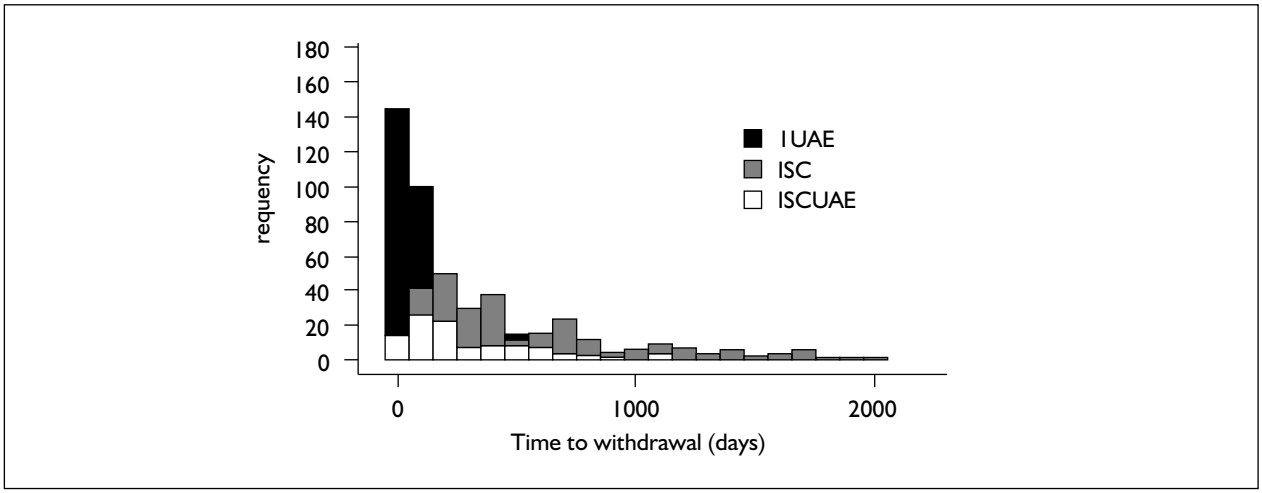


FIGURE 4 *Distribution of time to treatment failure for inadequate seizure control (ISC), unacceptable adverse events (UAEs) and ISC plus UAE (ISCUAE)*

seizures, neither of which reach statistical significance. After extensive investigation (detailed in Appendix 5), we have not been able to identify reasons for the trends for change in the primary outcomes through the course of the study. We suspect that there may be some difficulty in identifying learning effects of clinicians becoming more experienced with the use of newer agents, similar to effects observed during surgical studies. We have therefore presented data for OXC

TABLE 12 *Arm A – dose, as mean (standard deviation) range at withdrawal or last follow-up (excluding not epilepsy and children, entire recruitment period)*[a]

Reason for withdrawal	CBZ	GBP	LTG	TPM
ISC	*n* = 33 991 (347) 400–1800	*n* = 83 2414 (899) 300–4800	*n* = 42 355 (175) 85–800	*n* = 40 291 (168) 50–600
UAE	*n* = 50 546 (189) 200–1000	*n* = 35 1366 (636) 400–3000	*n* = 30 178 (113) 25–550	*n* = 68 137 (77) 25–400
ISC and UAE	*n* = 18 711 (323) 200–1400	*n* = 23 1878 (875) 600–3600	*n* = 9 219 (178) 50–550	*n* = 16 218 (110) 75–400
Other reason for withdrawal	*n* = 13 569 (317) 200–1200	*n* = 14 1314 (466) 300–2100	*n* = 19 184 (62) 50–300	*n* = 14 189 (103) 75–500
Remission of seizures	*n* = 14 614 (337) 200–1400	*n* = 12 1475 (663) 300–2700	*n* = 9 158 (92) 50–300	*n* = 13 133 (57) 50–200
Still on randomised drug	*n* = 140 662 (311) 100–2000	*n* = 120 1496 (669) 300–3600	*n* = 168 249 (136) 20–800	*n* = 126 181 (108) 25–600

[a] Dose data are missing for a number of patients. For this subset of patients with missing dose data, time to withdrawal tends to be shorter and reason for withdrawal more likely to be UAE or other reasons compared with those we have dose data for. Dose data in this table should be interpreted with this in mind.

TABLE 13 *Arm A – dose, as mean (standard deviation) range, at withdrawal or last follow-up (excluding not epilepsy and children, recruitment after June 2001 only)*[a]

Reason for withdrawal	CBZ	GBP	LTG	OXC	TPM
ISC	*n* = 18 950 (440) 400–1800	*n* = 51 2296 (835) 300–4800	*n* = 24 311 (132) 100–500	*n* = 15 1480 (525) 300–2100	*n* = 21 235 (166) 50–600
UAE	*n* = 26 519 (196) 200–1000	*n* = 22 1373 (622) 400–2400	*n* = 15 192 (95) 50–400	*n* = 29 895 (351) 300–2100	*n* = 32 113 (55) 25–250
ISC and UAE	*n* = 7 600 (400) 200-1400	*n* = 12 1933 (897) 600–3600	*n* = 7 239 (198) 50–550	*n* = 9 1150 (525) 450–1950	*n* = 10 200 (106) 75–400
Other reason for withdrawal	*n* = 4 475 (222) 300-800	*n* = 4 1425 (450) 1200–2100	*n* = 12 175 (72) 50–300	*n* = 7 814 (285) 600–1200	*n* = 7 175 (69) 75–300
Remission of seizures	*n* = 3 600 (200) 400-800	*n* = 2 1950 (1061) 1200–2700	*n* = 3 233 (115) 100–300	*n* = 7 771 (293) 300–1200	*n* = 5 125 (56) 50–200
Still on randomised drug	*n* = 93 626 (276) 200–2000	*n* = 70 1453 (701) 300–3600	*n* = 93 217 (108) 20–500	*n* = 87 1019 (467) 300–2850	*n* = 83 179 (109) 25–600

[a] Dose data are missing for a number of patients. For this subset of patients with missing dose data, time to withdrawal tends to be shorter and reason for withdrawal more likely to be UAE or other reasons compared with those we have dose data for. Dose data in this table should be interpreted with this in mind.

comparisons against patients restricted to those randomised to Arm A after 1 June 2001 (the primary and conservative estimate).

Time to treatment failure

This important outcome combines tolerability, and to some degree safety, with gains from seizure control. Results of ITT analyses are presented in *Figures 5–10* along with estimates of hazard ratios (HRs) and differences from CBZ, the standard drug comparator. The figures also explore the contributions to treatment failure from UAEs and ISC. Again, comparisons are presented with HRs and differences from CBZ.

There is great consistency across these analyses. For time to treatment failure for any reason (ISC or UAEs), there are significant overall differences, although inevitably there is some reduction in power in analyses using data from 1 June 2001 onwards. There is consistency in the ranking of drugs, with LTG being superior in all cases and GBP and TPM being the poorest performing drugs. When comparisons are made across the whole randomisation period, LTG is superior to all other drugs for pair-wise HR comparisons. CBZ and OXC are consistently intermediate between these options and appear broadly similar, although the CIs for HRs between CBZ and OXC are wide and should not be taken to imply equivalence between the two drugs.

Sensitivity analyses (not shown) indicate that including only patients with definite partial seizures and including patients subsequently withdrawn as 'not epilepsy' does not influence the results. A strict PP analysis also has little effect, as would be expected for this outcome, given the small number of patients excluded for this outcome.

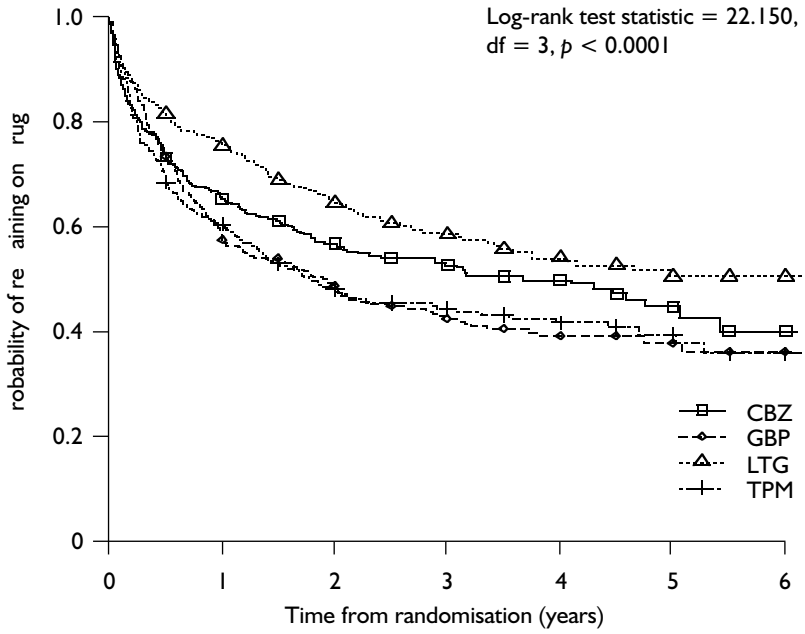
The cumulative incidence analyses show that the contributions to the treatment failure outcome vary according to the drug in question. Thus CBZ is the drug that is most frequently associated with treatment failure for UAEs, and LTG and GBP are least likely to produce this treatment failure, with TPM intermediate. In contrast, GBP is most likely to be associated with treatment failure due to ISC, and CBZ the least likely, with LTG and TPM being intermediate. When LTG is compared with CBZ, it is 10–11% superior for treatment withdrawal for adverse events and statistically different at all points between 1 and 6 years. It is similar to CBZ for incidence of treatment failure due to ISC, with point estimates varying between 1% superiority at 6 years and 6% inferiority at 4 years. For this efficacy outcome, examination of the lower 95% CI around point estimates for differences in withdrawal rates indicates that we have excluded any inferiority of LTG greater than 12% (years 4 and 5). At other time points, non-inferiority limits (according to the lower 95% CI) were 4% at 1 year, 8% at 2 years and 9% at 6 years. This could be taken as some evidence in support of non-inferiority for efficacy of LTG in comparison with CBZ.

Similar cumulative incidence analyses have been undertaken for the period after 1 June 2001 so as to allow some comparison of OXC with other drugs. Again, CBZ is the drug most likely to be associated with treatment failure due to unacceptable side-effects, but OXC would seem to have a better tolerability profile than CBZ and appears more like LTG in this respect. However, ISC is again least likely to give rise to treatment failure for CBZ, but OXC is somewhat poorer than CBZ for this outcome. Point estimates for treatment failure vary between 4% inferiority for OXC versus CBZ (years 1–3) and 6% at 4 years. Estimates do not exclude OXC being between 9% inferior at 1 year and 17% inferior at 4 years. This would not seem to support a claim for non-inferiority of OXC compared with CBZ for this efficacy outcome, although this may simply be due to the reduced power because of the fewer patients available for this analysis.

Time to 12-month remission

Results of analyses are presented in *Figures 11–14*. Again, comparisons are made using pair-wise HRs and differences from CBZ, the standard drug. We also present PP analyses in addition to ITT analysis.

The ITT analyses of the primary efficacy outcome in the study again show that times to achieve a 1-year remission of epilepsy are statistically different across all the drugs and identify GBP and TPM as the least favoured options. For GBP, the differences from CBZ (and indeed OXC and LTG) are consistent and of statistical significance and of likely clinical importance, although the differences for TPM from these drugs are less and fail to achieve statistical significance. The standard drug, CBZ, appears to be the preferred drug for this outcome in all pair-wise comparisons, with the possible exception of that against OXC. Here data restricted to the period from the period June 2001 suggest broad similarity between CBZ and OXC. Again, there are no consistent differences found when analysis is restricted to patients with definitely diagnosed partial epilepsy syndromes.

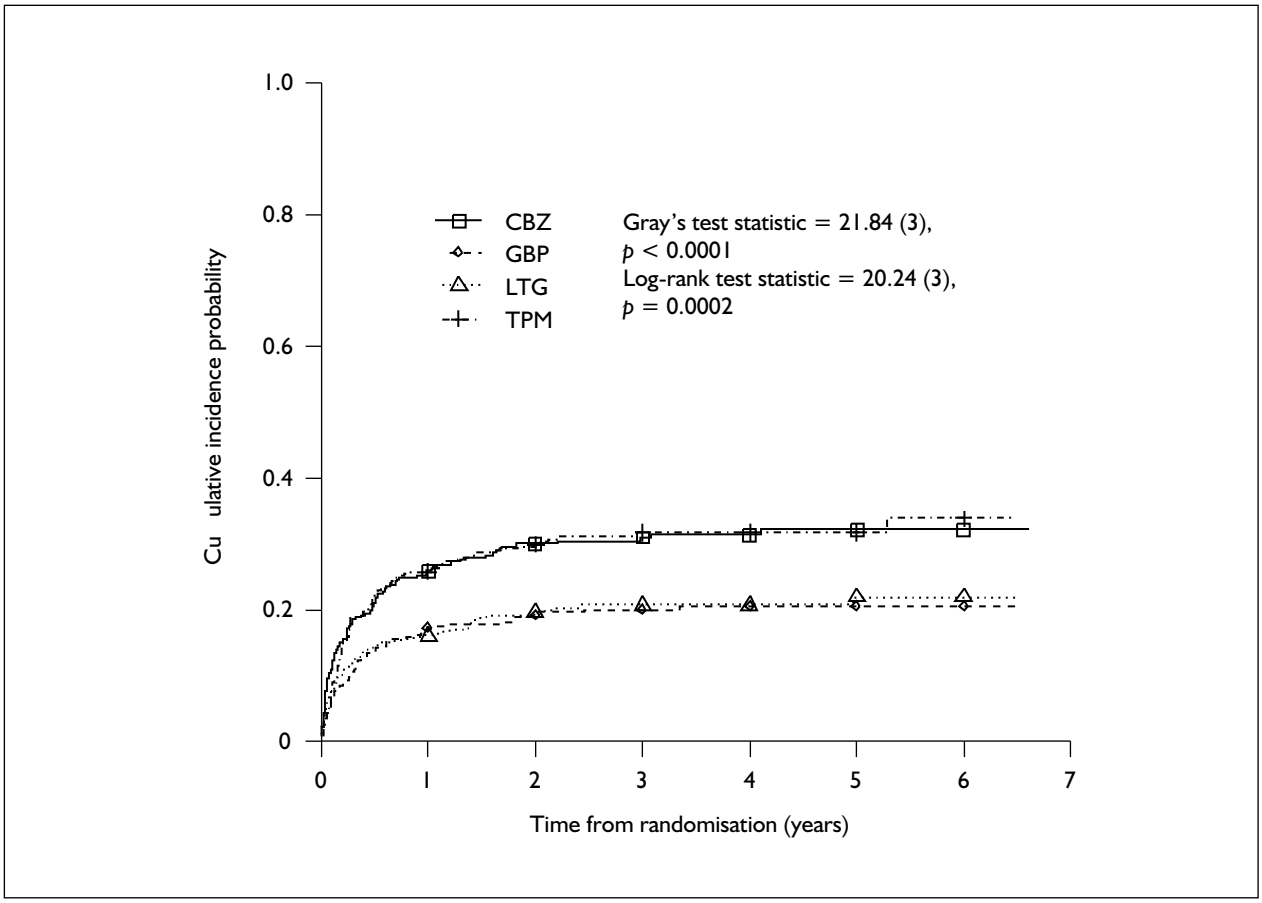


Drug (events/ total)		Year					
		1	2	3	4	5	6
CBZ (174/368)	Number at risk	225	160	106	65	26	7
	% still on drug (95% CI)	65 (61 to 70)	57 (52 to 62)	53 (47 to 58)	50 (44 to 56)	45 (38 to 52)	40 (31 to 49)
GBP (202/366)	Number at risk	195	133	87	51	24	8
	Difference in % still on drug compared with CBZ (95% CI)	–8 (–15 to –1)	–8 (–16 to –1)	–10 (–18 to –2)	–11 (–19 to –3)	–7 (–16 to 2)	–4 (–15 to 7)
LTG (151/370)	Number at risk	266	178	121	84	42	11
	Difference in % still on drug compared with CBZ (95% CI)	12 (6 to 19)	8 (1 to 15)	6 (–2 to 13)	4 (–4 to 12)	6 (–4 to 15)	11 (1 to 20)
TPM (198/366)	Number at risk	207	136	81	54	24	7
	Difference in % still on drug compared with CBZ (95% CI)	–5 (–12 to 2)	–9 (–16 to –2)	–8 (–16 to –1)	–8 (–16 to 0)	–5 (–14 to 4)	–4 (–16 to 7)

HR[a] (95% CI)	Baseline drug			
	CBZ	GBP	LTG	TPM
CBZ	–	0.83 (0.68 to 1.02)	*1.28 (1.03 to 1.60)*	0.82 (0.67 to 1.01)
GBP	1.21 (0.99 to 1.48)	–	*1.55 (1.25 to 1.91)*	0.99 (0.82 to 1.21)
LTG	*0.78 (0.63 to 0.97)*	*0.65 (0.52 to 0.80)*	–	*0.64 (0.52 to 0.79)*
TPM	1.22 (0.99 to 1.49)	1.01 (0.83 to 1.23)	*1.56 (1.26 to 1.93)*	–

[a] HR > 1 indicates that failure occurs more rapidly on drug compared with baseline. Italic indicates clinical significance.

FIGURE 5 *Time to treatment failure (Arm A) for entire recruitment period*

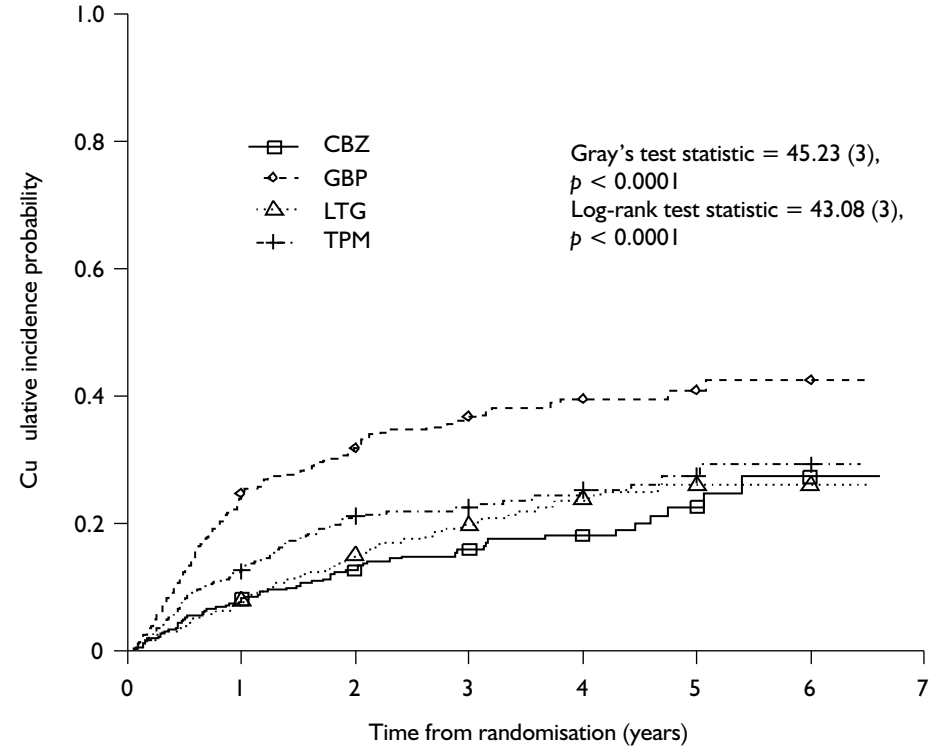


Drug (events/ total)		Year					
		1	**2**	**3**	**4**	**5**	**6**
CBZ (111/368)	% still on drug (95% CI)	74 (70 to 79)	70 (65 to 75)	69 (64 to 74)	69 (64 to 74)	68 (63 to 73)	68 (63 to 73)
GBP (71/366)	Difference in % still on drug compared with CBZ (95% CI)	9 (3 to 15)	11 (4 to 17)	11 (4 to 17)	11 (4 to 17)	12 (5 to 18)	12 (5 to 18)
LTG (74/370)		10 (4,16)	11 (4 to 17)	10 (4 to 17)	11 (4 to 17)	10 (3 to 17)	10 (3 to 17)
TPM (110/366)		0 (–6 to 6)	0 (–7 to 7)	–1 (–8 to 6)	0 (–7 to 7)	1 (–7 to 8)	–2 (–10 to 7)

HR[a] (95% CI)	**Baseline drug**			
	CBZ	**GBP**	**LTG**	**TPM**
CBZ	–	*1.67 (1.24 to 2.25)*	*1.61 (1.20 to 2.17)*	1.01 (0.77 to 1.31)
GBP	*0.60 (0.44 to 0.81)*	–	0.96 (0.70 to 1.34)	*0.60 (0.45 to 0.81)*
LTG	*0.62 (0.46 to 0.83)*	*1.04 (0.75 to 1.44)*	–	*0.62 (0.46 to 0.84)*
TPM	0.99 (0.77 to 1.30)	*1.66 (1.24 to 2.24)*	*1.60 (1.20 to 2.15)*	–

[a] HR > 1 indicates that failure occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 6 *Time to treatment failure (Arm A) for entire recruitment period – cumulative incidence for UAE (ISC + UAE counted as ISC)*

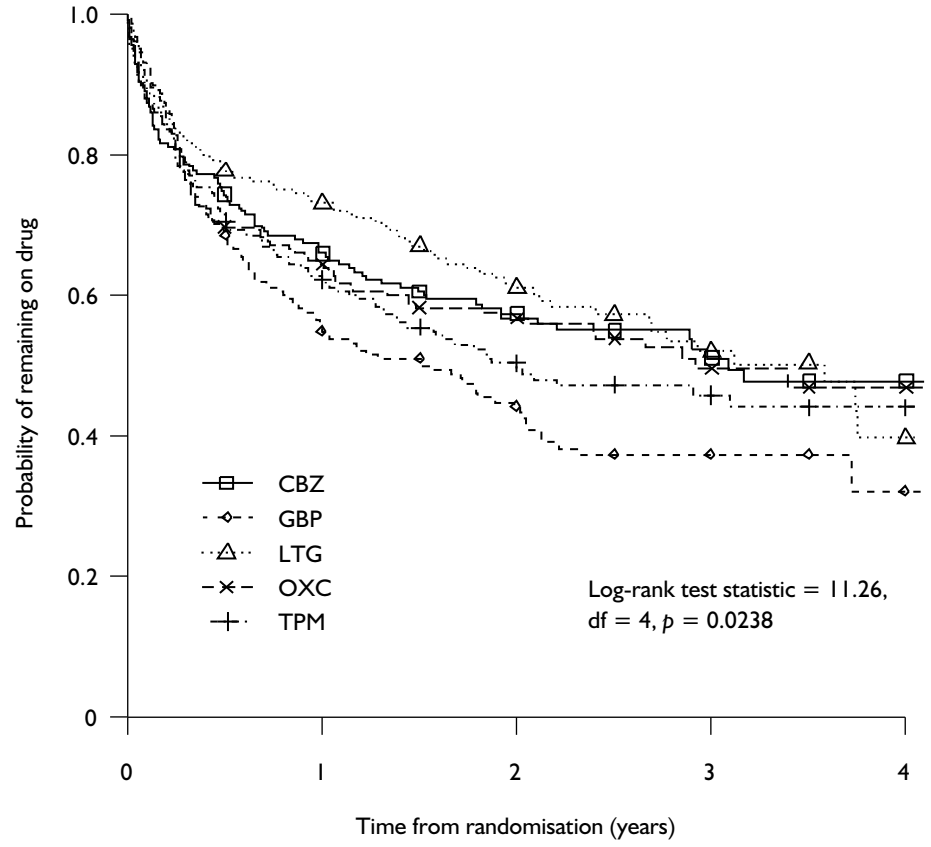


Drug (events/ total)		Year					
		1	2	3	4	5	6
CBZ (61/368)	% still on drug (95% CI)	92 (55 to 95)	87 (41 to 91)	84 (33 to 88)	82 (28 to 86)	77 (20 to 83)	73 (15 to 81)
GBP (128/366)	Difference in % still on drug compared with CBZ (95% CI)	–17 (–22 to –11)	–19 (–25 to –13)	–21 (–27 to –14)	–21 (–29 to –14)	–18 (–27 to –10)	–15 (–26 to –4)
LTG (72/370)		0 (–4 to 4)	–2 (–8 to 3)	–4 (–10 to 2)	–6 (–12 to 1)	–3 (–12 to 5)	1 (–9 to 12)
TPM (81/366)		–4 (–9 to 0)	–8 (–14 to –3)	–7 (–13 to 0)	–7 (–14 to 0)	–5 (–13 to 4)	–2 (–13 to 9)

HR[a] (95% CI)	Baseline drug			
	CBZ	GBP	LTG	TPM
CBZ	–	*0.41 (0.30 to 0.55)*	0.85 (0.61 to 1.19)	*0.70 (0.50 to 0.98)*
GBP	*2.45 (1.81, 3.32)*	–	*2.09 (1.57 to 2.79)*	*1.72 (1.30 to 2.28)*
LTG	1.17 (0.84 to 1.64)	*0.48 (0.36 to 0.64)*	–	0.82 (0.60 to 1.12)
TPM	*1.43 (1.03 to 1.98)*	*0.58 (0.44 to 0.77)*	1.22 (0.89 to 1.67)	–

[a] HR > 1 indicates that failure occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 7 *Time to treatment failure (Arm A) for entire recruitment period – cumulative incidence for ISC (ISC + UAE counted as ISC)*

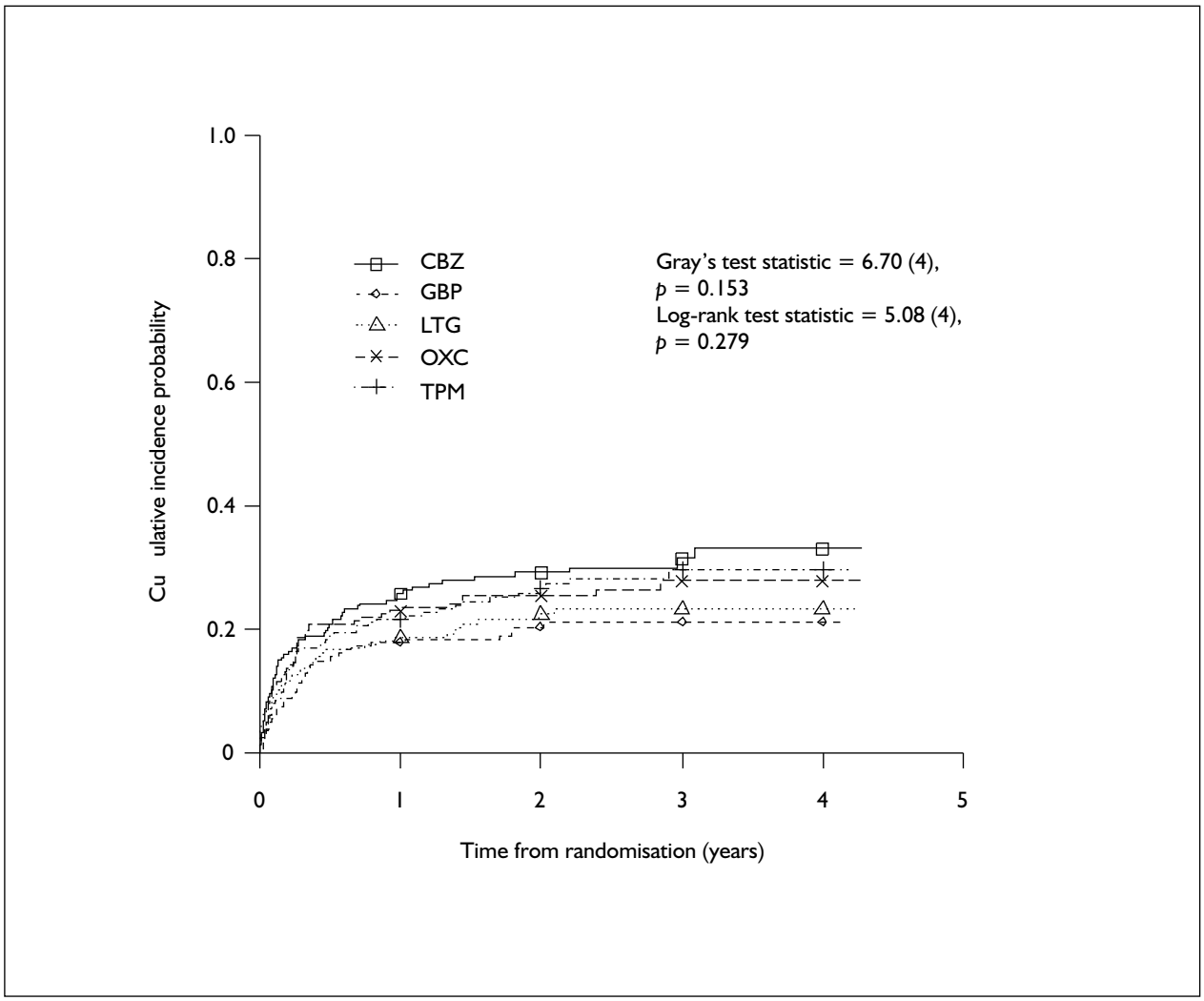


Drug (events/ total)		Year			
		1	2	3	4
CBZ (93/207)	Number at risk	129	80	36	3
	% still on drug (95% CI)	66 (59 to 72)	57 (50 to 64)	51 (43 to 59)	48 (39 to 56)
OXC (90/202)	Number at risk	118	73	29	3
	Difference in % still on drug compared with CBZ (95% CI)	–2 (–11 to 8)	–1 (–11 to 9)	–1 (–13 to 10)	–1 (–14 to 12)

HR[a] (95% CI)	Baseline drug				
	CBZ	GBP	LTG	OXC	TPM
OXC	1.04 (0.78 to 1.39)	*0.75 (0.57 to 0.98)*	1.15 (0.86 to 1.54)	–	0.90 (0.68 to 1.19)

[a] HR > 1 indicates that failure occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 8 *Time to treatment failure excluding (Arm A) for recruitment after June 2001*

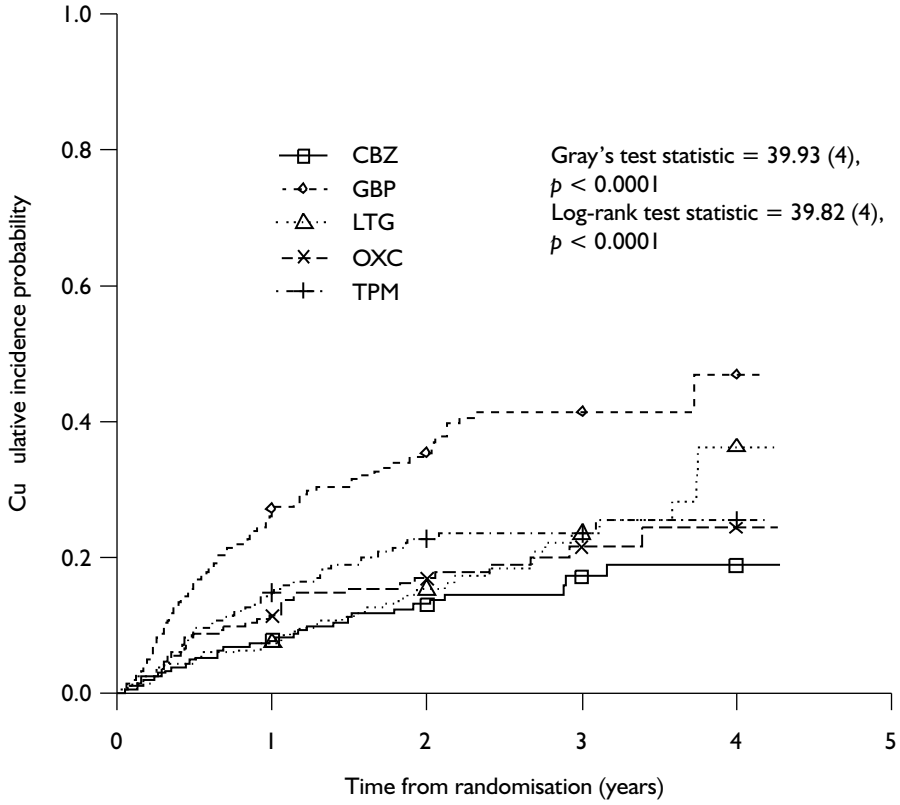


Drug (events/ total)		Year			
		1	2	3	4
CBZ (62/207)	% still on drug (95% CI)	74 (68 to 80)	71 (64 to 77)	69 (62 to 75)	67 (60 to 74)
OXC (51/202)	Difference in % still on drug compared with CBZ (95% CI)	3 (–6 to 11)	4 (–5 to 13)	4 (–6 to 13)	5 (–5 to 15)

HR[a] (95% CI)	Baseline drug				
	CBZ	GBP	LTG	OXC	TPM
OXC	0.85 (0.59 to 1.24)	1.36 (0.90 to 2.05)	1.21 (0.81 to 1.81)	–	0.98 (0.67 to 1.44)

[a] HR > 1 indicates that failure occurs more rapidly on drug compared with baseline.

FIGURE 9 *Time to treatment failure (Arm A) for recruitment after June 2001 – cumulative incidence for UAE (ISC + UAE counted as ISC)*

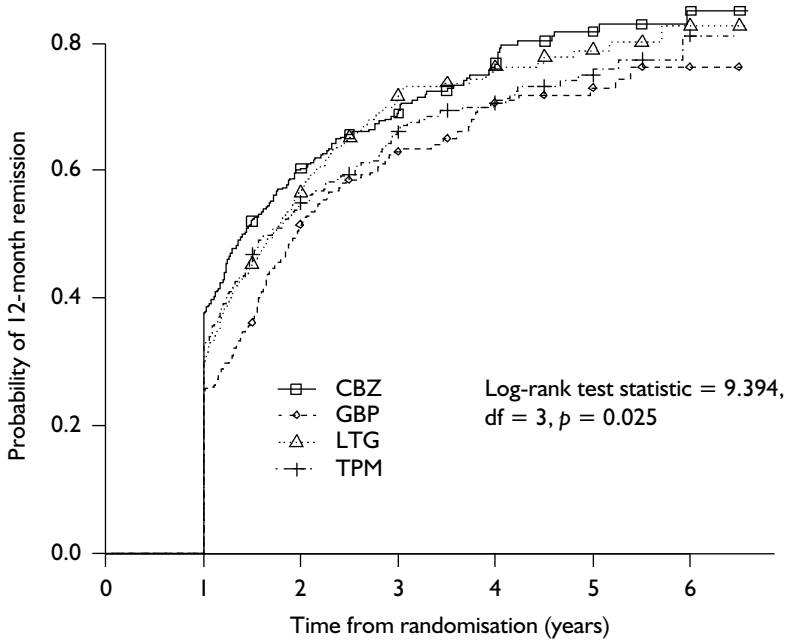


Drug (events/ total)		Year			
		1	2	3	4
CBZ(30/207)	% still on drug (95% CI)	92 (88 to 96)	87 (82 to 92)	83 (77 to 89)	81 (74 to 88)
OXC (36/202)	Difference in % still on drug compared with CBZ (95% CI)	–4 (–9 to 2)	–4 (–11 to 4)	–4 (–14 to 5)	–6 (–17 to 5)

HR[a] (95% CI)	Baseline drug				
	CBZ	GBP	LTG	OXC	TPM
OXC	1.33 (0.82 to 2.15)	*0.43 (0.29 to 0.64)*	0.99 (0.63, 1.54)	–	0.82 (0.53 to 1.28)

[a] HR > 1 indicates that failure occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 10 *Time to treatment failure excluding (Arm A) for recruitment after June 2001 – cumulative incidence for ISC (ISC + UAE counted as ISC)*

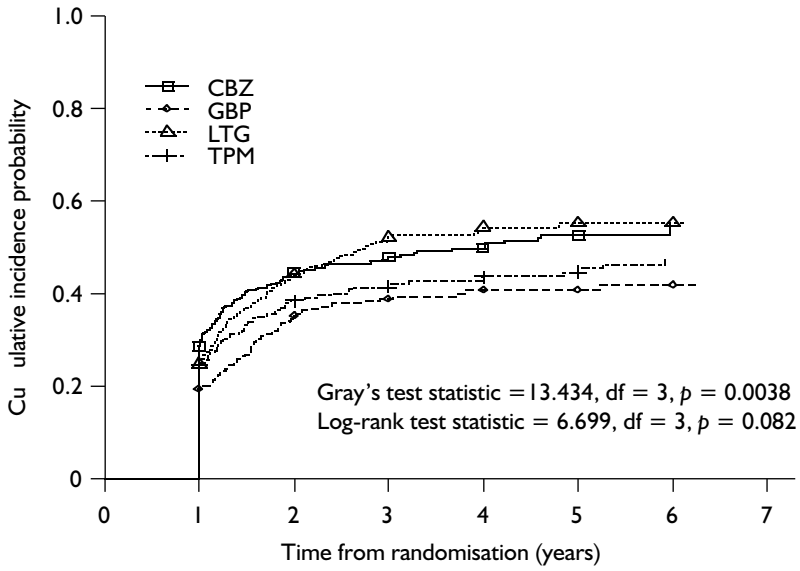


Drug (events/ total)		Year					
		1	2	3	4	5	6
CBZ (254/362)	Number at risk	347	120	73	41	16	6
	% 12-month remission (95% CI)	36 (31 to 41)	60 (55 to 66)	69 (63 to 74)	77 (72 to 82)	82 (77 to 87)	85 (79 to 91)
GBP (215/359)	Number at risk	337	141	76	45	25	7
	Difference in % 12-month remission compared with CBZ (95% CI)	–12 (– 19 to –5)	–9 (–16 to –1)	–6 (–13 to 2)	–6 (–14 to 1)	–9 (–17 to –1)	–9 (–18 to 0)
LTG (245/365)	Number at risk	356	126	59	36	19	4
	Difference in % 12-month remission compared with CBZ (95% CI)	–7 (–13 to 0)	–3 (–11 to 4)	3 (–4 to 11)	–1 (–8 to 7)	–3 (–10 to 5)	–2 (–11 to 7)
TPM (225/358)	Number at risk	338	126	74	50	24	5
	Difference in % 12-month remission compared with CBZ (95% CI)	–3 (–10 to 4)	–5 (–13 to 2)	–2 (–10 to 5)	–6 (–14 to 1)	–7 (–14 to 1)	–4 (–14 to 6)

HR[a] (95% CI)	Baseline drug			
	CBZ	GBP	LTG	TPM
CBZ	–	*1.33 (1.11 to 1.60)*	1.10 (0.92 to 1.31)	1.17 (0.98 to 1.40)
GBP	*0.75 (0.63 to 0.90)*	–	*0.82 (0.69 to 0.99)*	0.88 (0.73 to 1.06)
LTG	0.91 (0.77 to 1.09)	*1.21 (1.01 to 1.46)*	–	1.06 (0.89 to 1.28)
TPM	0.86 (0.72 to 1.03)	1.14 (0.95 to 1.37)	0.94 (0.78 to 1.13)	–

[a] HR > 1 indicates that 12-month remission occurs more rapidly on drug compared with baseline insert. Italic indicates statistical significance.

FIGURE 11 *Time to 12-month remission (Arm A) for entire recruitment period*

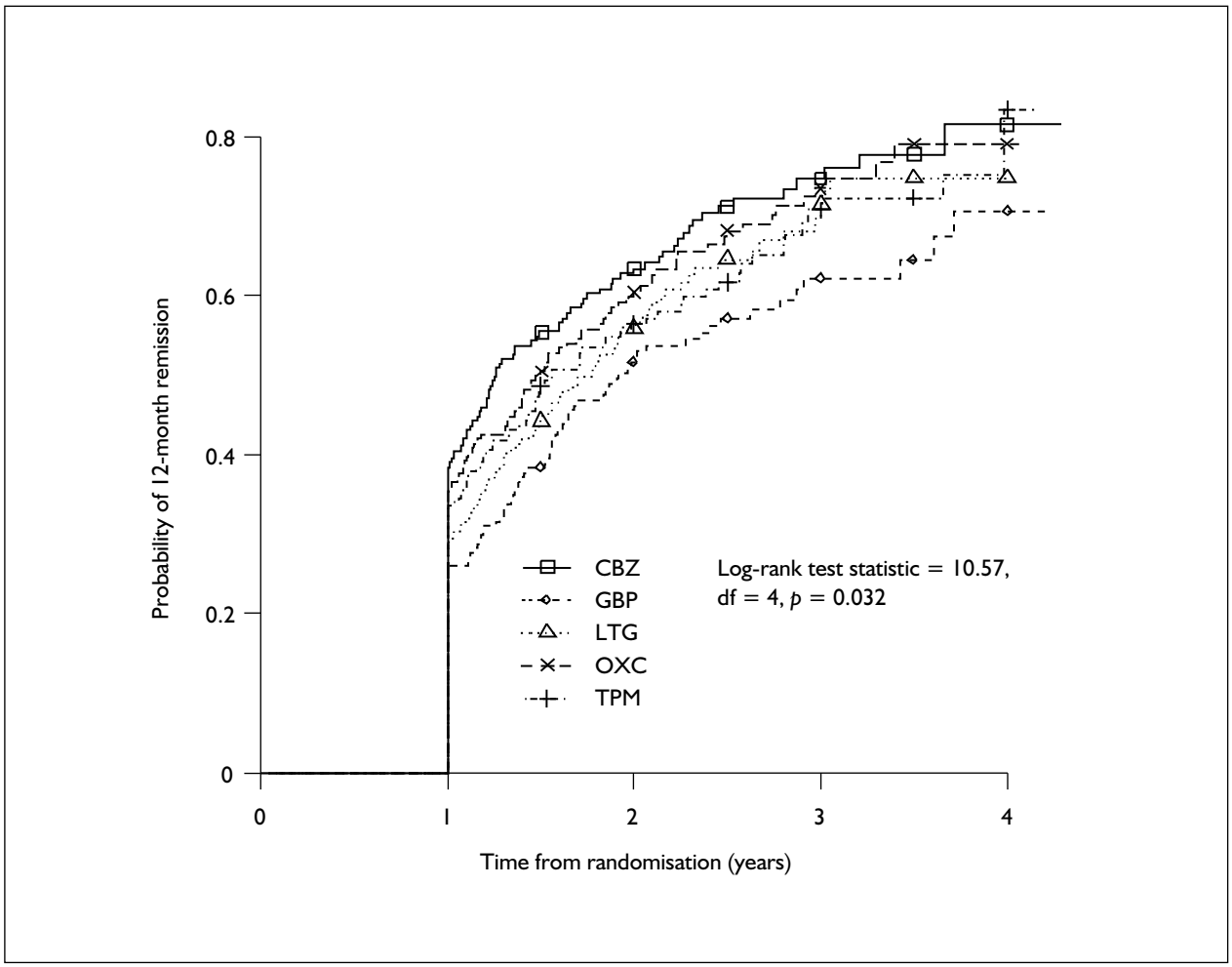


Drug (events/ total)		Year				
		1	2	3	4	5
CBZ (164/352)	Number at risk	222	47	26	13	5
	% 12-month remission (95% CI)	29 (24 to 34)	44 (39 to 50)	48 (42 to 53)	50 (44 to 55)	53 (47 to 58)
GBP (126/351)	Number at risk	194	42	16	8	5
	Difference in % 12-month remission compared with CBZ (95% CI)	–9 (–16 to –3)	–9 (–17 to –2)	–9 (–17 to –1)	–9 (–17 to –1)	–12 (–20 to –4)
LTG (170/358)	Number at risk	264	66	25	16	6
	Difference in % 12-month remission compared with CBZ (95% CI)	–4 (–11 to 3)	0 (–8 to 7)	4 (–4 to 12)	5 (–3 to 12)	3 (–5 to 11)
TPM (138/353)	Number at risk	203	40	15	5	3
	Difference in % 12-month remission compared with CBZ (95% CI)	–4 (–11 to 3)	–6 (–13 to 2)	–6 (–14 to 1)	–6 (–14 to 2)	–8 (–16 to 0)

HR[a] (95% CI)	Baseline drug			
	CBZ	GBP	LTG	TPM
CBZ	–	*1.39 (1.12 to 1.73)*	0.99 (0.82 to 1.21)	*1.23 (1.00 to 1.52)*
GBP	*0.72 (0.58 to 0.89)*	–	*0.71 (0.58 to 0.88)*	0.88 (0.70 to 1.11)
LTG	1.01 (0.83 to 1.22)	*1.41 (1.14 to 1.74)*	–	*1.24 (1.01 to 1.52)*
TPM	*0.81 (0.66 to 1.00)*	1.13 (0.90 to 1.42)	*0.81 (0.66 to 0.99)*	–

[a] HR > 1 indicates that 12-month remission occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 12 *Time to 12-month remission (Arm A) for entire recruitment period as PP analysis*

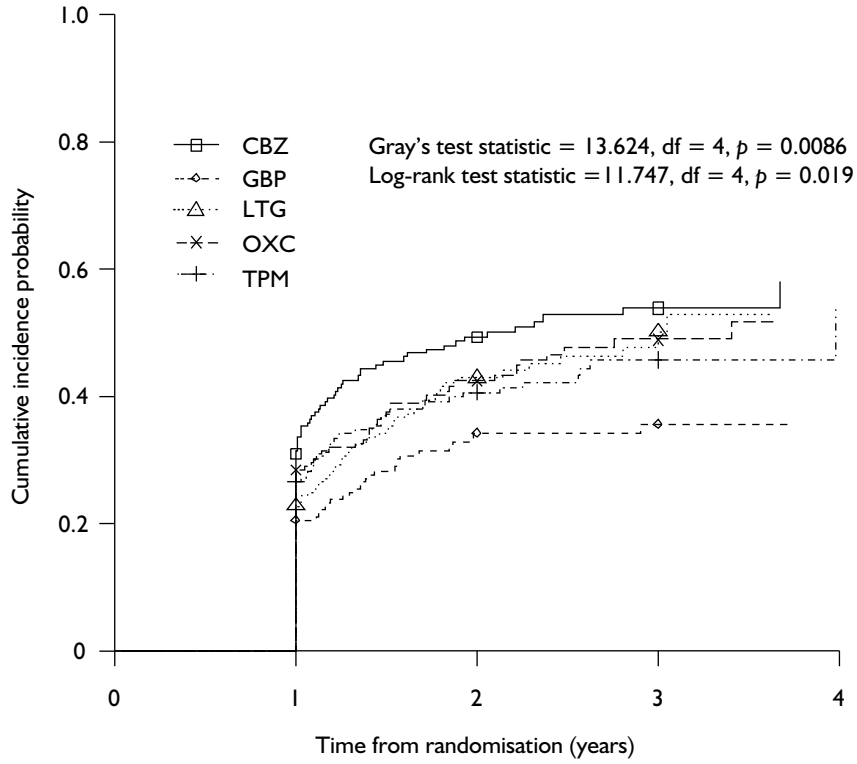


Drug (events/ total)		Year			
		1	2	3	4
CBZ (135/206)	Number at risk	195	55	19	3
	% 12-month remission (95% CI)	36 (30 to 43)	63 (56 to 70)	75 (67 to 82)	81 (72 to 90)
OXC (128/200)	Number at risk	189	58	21	3
	Difference in % 12-month remission compared with CBZ (95% CI)	–1 (–11 to 9)	–3 (–13 to 7)	–1 (–12 to 9)	–2 (–15 to 10)

HR[a] (95% CI)	Baseline drug				
	CBZ	GBP	LTG	OXC	TPM
OXC	0.92 (0.73 to 1.18)	*1.37 (1.06 to 1.78)*	1.15 (0.89 to 1.47)	–	1.10 (0.86 to 1.42)

[a] HR > 1 indicates that 12-month remission occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 13 *Time to 12-month remission (Arm A) for recruitment after June 2001*



Drug (events/ total)		Year		
		1	2	3
CBZ (96/200)	Number at risk	128	18	5
	% 12-month remission (95% CI)	31 (24 to 38)	49 (42 to 57)	54 (46 to 61)
OXC (80/195)	Number at risk	117	25	6
	Difference in % 12-month remission compared with CBZ (95% CI)	–2 (–12 to 7)	–7 (–17 to 4)	–5 (–16 to 6)

HR[a] (95% CI)	Baseline drug				
	CBZ	GBP	LTG	OXC	TPM
OXC	0.84 (0.64 to 1.10)	*1.43 (1.06 to 1.95)*	1.03 (0.78 to 1.36)	–	1.07 (0.81 to 1.42)

[a] HR > 1 indicates that 12-month remission occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 14 *Time to 12-month remission (Arm A) for recruitment after June 2001 as PP analysis*

TABLE 14 *Arm A – summary of treatment taken when 12-month remission achieved (entire recruitment period)*[a]

Randomised drug	CBZ	GBP	LTG	OXC	TPM	CLB	LVT	PHT	VPS	Polytherapy	Total
CBZ	170 (73.9)	4 (1.7)	31 (13.5)	1 (0.4)	3 (1.3)	0	4 (1.7)	1 (0.4)	9 (3.9)	7 (3)	230[b] (100)
GBP	28 (14.7)	132 (69.1)	14 (7.3)	1 (0.5)	2 (1.0)	1 (0.5)	4 (2.1)	1 (0.5)	2 (1.0)	6 (3.1)	191[c] (100)
LTG	20 (9.4)	2 (0.9)	176 (83.0)	0	1 (0.5)	1 (0.5)	2 (0.9)	2 (0.9)	6 (2.8)	2 (0.9)	212[d] (100)
TPM	40 (19.7)	2 (1.0)	8 (3.9)	1 (0.5)	143 (70.4)	0	2 (1.0)	1 (0.5)	2 (1.0)	4 (2.0)	203[e] (100)

CLB, clobazam; LVT, levetiracetam; PHT, phenytoin; VPS, valproate.
[a] Randomised drug if date of withdrawal occurred after date of 12-month remission and drug listed at visit prior to date of 12-month remission otherwise. If more than one drug listed at visit prior to date of 12-month remission, it may be possible that at the time of remission only one of the drugs was being taken. Data: *n* (%).
[b] No AED being taken or no information on AED at time of remission for 24 patients.
[c] No AED being taken or no information on AED at time of remission for 24 patients.
[d] No AED being taken or no information on AED at time of remission for 33 patients.
[e] No AED being taken or no information on AED at time of remission for 22 patients.

TABLE 15 *Arm A – summary of treatment taken when 12-month remission achieved (recruitment after June 2001)*[a]

Randomised drug	CBZ	GBP	LTG	OXC	TPM	LVT	PHT	VPS	Polytherapy	Total
CBZ	98 (78.4)	0	14 (11.2)	1 (0.8)	1 (0.8)	3 (2.4)	0	4 (3.2)	4 (3.2)	125[b] (100)
GBP	18 (18.9)	62 (65.3)	6 (6.3)	1 (1.1)	1 (1.1)	2 (2.1)	0	1 (1.1)	4 (1.1)	95[c] (100)
LTG	13 (13.0)	0	83 (83.0)	0	0	1 (1.0)	0	3 (3.0)	0	100[d] (100)
OXC	4 (3.5)	1 (0.9)	10 (8.7)	82 (71.3)	2 (1.7)	3 (2.6)	1 (0.9)	6 (5.2)	6 (5.2)	115[e] (100)
TPM	17 (16.2)	1 (1.0)	2 (1.9)	1 (1.0)	80 (76.2)	1 (1.0)	1 (1.0)	1 (1.0)	1 (1.1)	105[f] (100)

LVT, levetiracetam; PHT, phenytoin; VPS, valproate.
[a] Randomised drug if date of withdrawal occurred after date of 12-month remission and drug listed at visit prior to date of 12-month remission otherwise. If more than one drug listed at visit prior to date of 12-month remission, it may be possible that at the time of remission only one of the drugs was being taken. Date: *n* = (%)
[b] No AED being taken or no information on AED at time of remission for 10 patients.
[c] No AED being taken or no information on AED at time of remission for 11 patients.
[d] No AED being taken or no information on AED at time of remission for 20 patients.
[e] No AED being taken or no information on AED at time of remission for 13 patients.
[f] No AED being taken or no information on AED at time of remission for 11 patients.

In ITT analyses, follow-up data after a treatment failure have been included in the analysis. Thus some patients achieve a 1-year remission on drug regimes other than that to which they were randomised and still contribute to outcome for the drug to which patients were originally randomised. In examining data for ITT for time to 12-month remission, it becomes important to understand how clinicians chose to switch treatment after treatment failure events. This is described in *Tables 14* and *15*. It is evident that following failure on one of the newer drugs, it was most likely that remission would subsequently occur with switching to CBZ, but that following failure on CBZ, switching to LTG was most commonly offered.

For these reasons, a PP analysis is also presented in which observations were censored at the point of treatment failure (*Figures 12* and *14*) (a 1-year

remission is only counted as an event for patients achieving remission on the drug to which they were randomised). Overall, the best performing drugs result in approximately 50% of patients achieving a 1-year remission on the drug to which they were randomised in comparison with approximately 75% remission rates for the best performing drugs in the ITT analyses (at 1500 days after randomisation). For the comparisons across the whole treatment period, differences between CBZ and LTG appear small. Whereas the point estimates suggest a 4% inferiority for LTG at 1 year, there is no difference at 2 years and LTG is superior at 4–5 years. Examination of the lower 95% CI around point estimates indicates that there is sufficient power in these comparisons to exclude LTG being any more than 11% inferior to CBZ at 1 year, 8% at 2 years, 4% at 3 years, 3% at 4 years and 5% at 5 years after randomisation. These estimates may be sufficient to support non-inferiority of LTG compared with CBZ for this primary efficacy outcome. It is this PP analysis which is most conservative when considering issues of non-inferiority.

When the PP analysis for the period after inclusion of OXC is considered, CBZ is again the preferred option. OXC produces similar 12-month remission rates but the 95% CIs do not exclude OXC being 12% (at 1 year) to 17% (at 2 years) inferior to CBZ. There is insufficient evidence of non-inferiority.

Secondary clinical outcomes

Time to 24-month remission

This outcome may potentially be regarded as of greater clinical importance than time to 1-year remission and large numbers of patients did achieve this outcome, although the power to detect differences was smaller due to the smaller number of events.

ITT and PP analyses are presented in *Figures 15–18*.

The data for 2-year remission are similar to those for 1-year remission, although the numbers achieving this outcome are smaller. In the ITT analysis, CBZ is superior to all other drugs and statistically so for GBP and TPM. For the period after the addition of OXC, this drug appears statistically superior to GBP. CBZ remains the preferred option, but the observed differences in pair-wise comparisons between OXC and CBZ, LTG and TPM do not achieve significance.

For the PP analysis, LTG shows a trend towards superiority over CBZ at 4–6 years, when the whole recruitment period is considered. The 95% CIs exclude LTG being more than 11% inferior to CBZ (years 1 and 2) and 6–8% inferior (years 4–6). For the period after addition of OXC, there is a suggestion of similarity between this drug and CBZ, although the 95% CIs are very wide because of smaller numbers of patients and events.

Time to first seizure

The data for this outcome are presented in *Figures 19–22*. This is one of the outcomes recommended for consideration in ILAE consensus documents.[66] It is notable that the overall comparisons restricted to recruitment after June 2001 fail to achieve statistical significance.

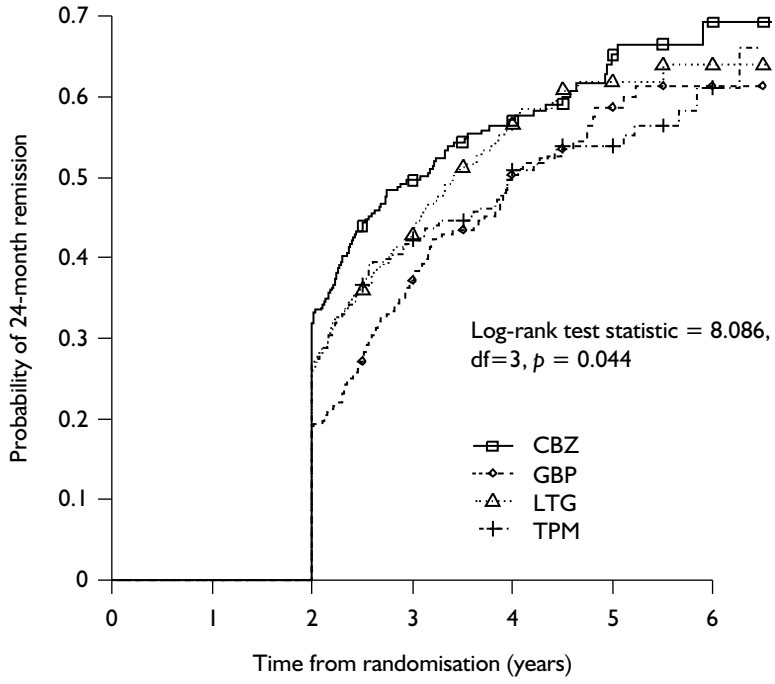
ITT analyses of time to first seizure after randomisation will be dependent on both the efficacy of the drug and initial dosing. Issues relating to drug dosing will be addressed below, but there is again a consistency of results. GBP appears least effective in preventing first seizures, with CBZ being most effective. TPM and LTG are intermediate. Pair-wise comparisons for the entire period show CBZ to be statistically superior to both GBP and LTG, but not TPM. For the period after addition of OXC, CBZ remains the preferred option but OXC produces similar outcomes.

PP analysis of the period following addition of OXC shows that 95% CIs do not exclude OXC being between 13 and 19% inferior to CBZ, too large a potential difference to allow a conclusion of non-inferiority.

Effects of age

The patients recruited to SANAD covered a wide range of ages and included children (age 5 years to below 16 years, $n = 163$) and elderly (65 years and over, $n = 150$). It is therefore possible to examine the effects of age on outcomes and test for any interaction between age and treatment effect for individual drugs, by comparing outcomes with the larger mid-life group ($n = 1162$). This is important given uncertainty about whether treatment effects are similar across the age groups and the fact that most RCTs in epilepsy are generally restricted to patients in the mid-life group.

For treatment failure, the main effect of age is statistically significant, change in $-2\log L$ (where L = likelihood) = 10.839 [on 2 degrees of freedom (df), $p = 0.0044$] with results suggesting that children (age < 16 years) are significantly more likely to experience treatment failure [HR (95%

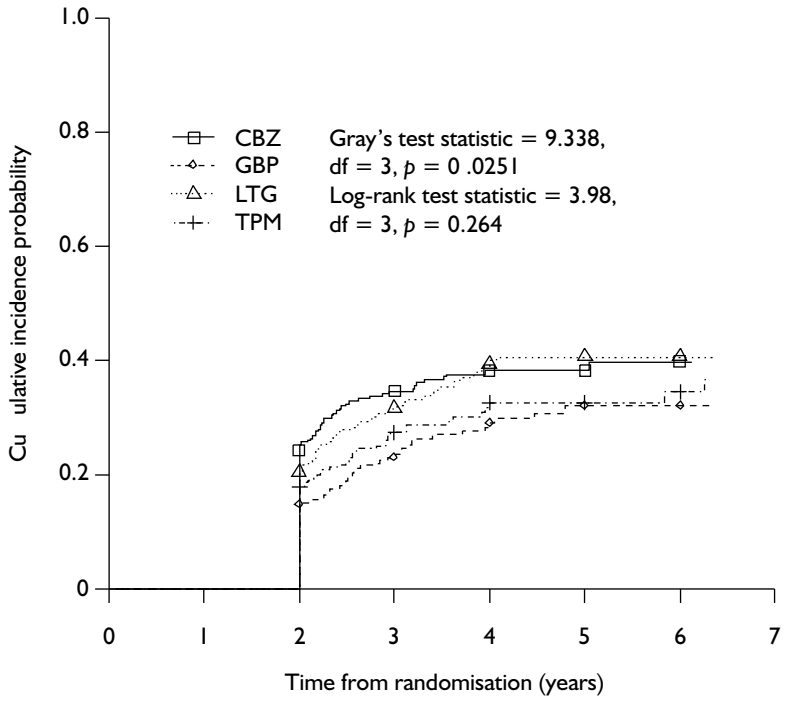


Drug (events/ total)		Year				
		2	3	4	5	6
CBZ (168/362)	Number at risk	295	116	71	28	8
	% 24-month remission (95% CI)	32 (27 to 37)	50 (44 to 56)	57 (51 to 63)	65 (58 to 72)	69 (61 to 78)
GBP (132/359)	Number at risk	283	125	74	36	8
	Difference in % 24-month remission compared with CBZ (95% CI)	–13 (–20 to –6)	–12 (–21 to –4)	–7 (–16 to 2)	–7 (–17 to 4)	–8 (–20 to 4)
LTG (155/365)	Number at risk	296	120	67	30	9
	Difference in % 24-month remission compared with CBZ (95% CI)	–6 (–13 to 1)	–7 (–15 to 1)	–1 (–9 to 8)	–3 (–13 to 6)	–5 (–17 to 6)
TPM (140/358)	Number at risk	284	124	80	41	12
	Difference in % 24-month remission compared with CBZ (95% CI)	–5 (–12 to 3)	–7 (–16 to 1)	–6 (–15 to 3)	–11 (–21 to –2)	–8 (–20 to 4)

HR[a] (95% CI)	Baseline drug			
	CBZ	GBP	LTG	TPM
CBZ	–	*1.39 (1.10 to 1.74)*	1.14 (0.91 to 1.41)	*1.26 (1.00 to 1.57)*
GBP	*0.72 (0.58 to 0.91)*	–	0.82 (0.65 to 1.03)	0.91 (0.71 to 1.15)
LTG	0.88 (0.71 to 1.10)	1.22 (0.97 to 1.54)	–	1.11 (0.88 to 1.39)
TPM	*0.80 (0.64 to 1.00)*	1.10 (0.87 to 1.40)	0.90 (0.72 to 1.14)	–

[a] HR > 1 indicates that 24-month remission occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 15 *Time to 24-month remission (Arm A) for entire recruitment period*

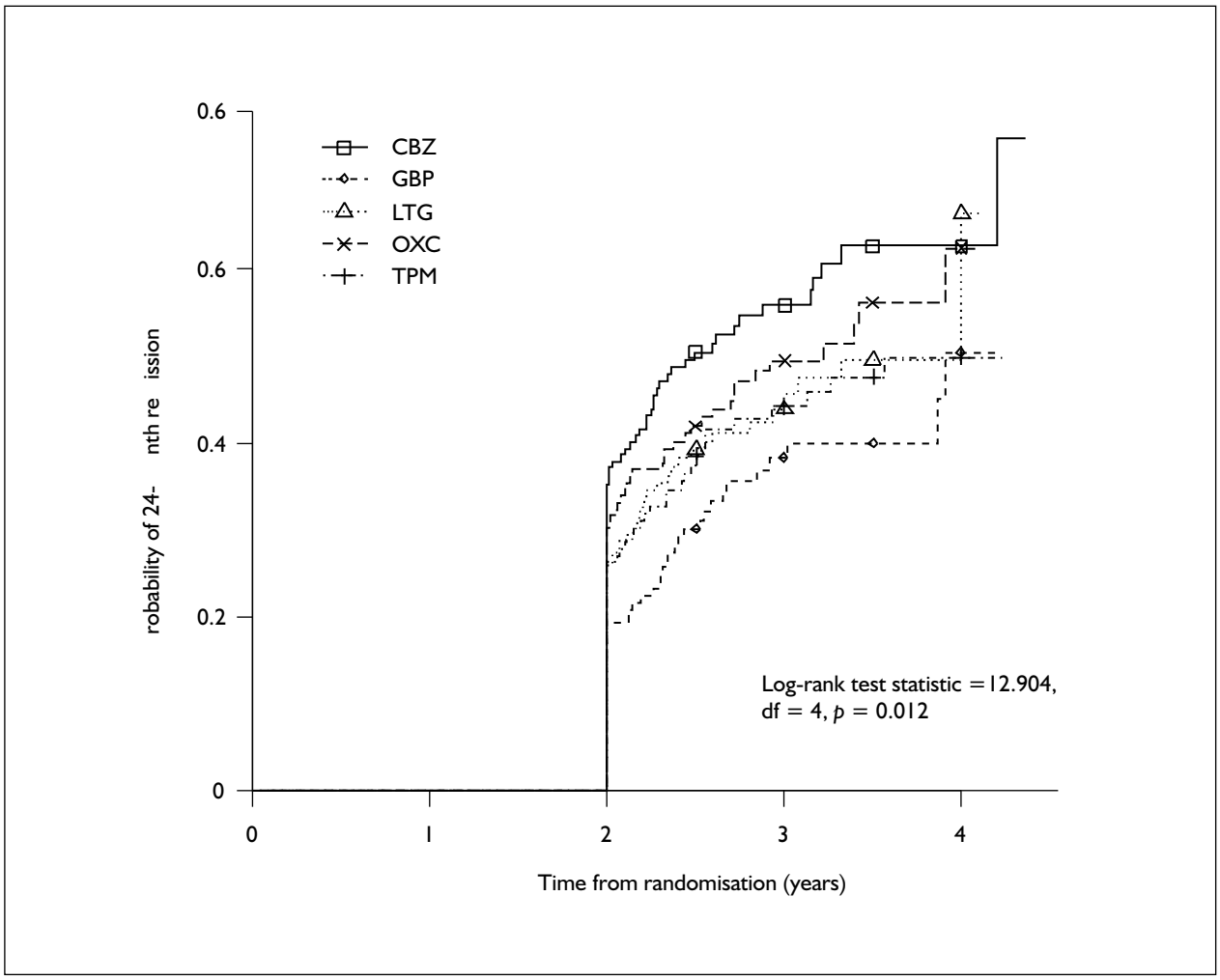


Drug (events/ total)		Year				
		2	**3**	**4**	**5**	**6**
CBZ (99/352)	Number at risk	156	47	25	11	1
	% 24-month remission (95% CI)	24 (19 to 29)	35 (29 to 40)	38 (32 to 44)	38 (32 to 44)	40 (33 to 46)
GBP (71/351)	Number at risk	131	39	18	7	2
	Difference in % 24-month remission compared with CBZ (95% CI)	–9 (–16 to –3)	–12 (–19 to –4)	–9 (–17 to –1)	–6 (–15 to 2)	–8 (–17 to 1)
LTG (96/358)	Number at risk	176	59	32	12	4
	Difference in % 24-month remission compared with CBZ (95% CI)	–4 (–11 to 3)	–3 (–11 to 5)	1 (–7 to 10)	2 (–6 to 11)	1 (–8 to 10)
TPM (78/353)	Number at risk	135	33	14	9	4
	Difference in % 24-month remission compared with CBZ (95% CI)	–6 (–13 to 0)	–7 (–15 to 1)	–6 (–14 to 3)	–6 (–14 to 3)	–5 (–15 to 4)

HR[a] (95% CI)	**Baseline drug**			
	CBZ	**GBP**	**LTG**	**TPM**
CBZ	–	*1.46 (1.10 to 1.93)*	1.04 (0.81 to 1.34)	*1.31 (1.00 to 1.72)*
GBP	*0.69 (0.52 to 0.91)*	–	*0.71 (0.54 to 0.95)*	0.90 (0.67 to 1.21)
LTG	0.96 (0.74 to 1.24)	*1.40 (1.06 to 1.85)*	–	1.25 (0.96 to 1.65)
TPM	*0.77 (0.58 to 1.00)*	1.16 (0.83 to 1.50)	0.80 (0.61 to 1.05)	–

[a] HR > 1 indicates that 24-month remission occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 16 *Time to 24-month remission (Arm A) for entire recruitment period as PP analysis*

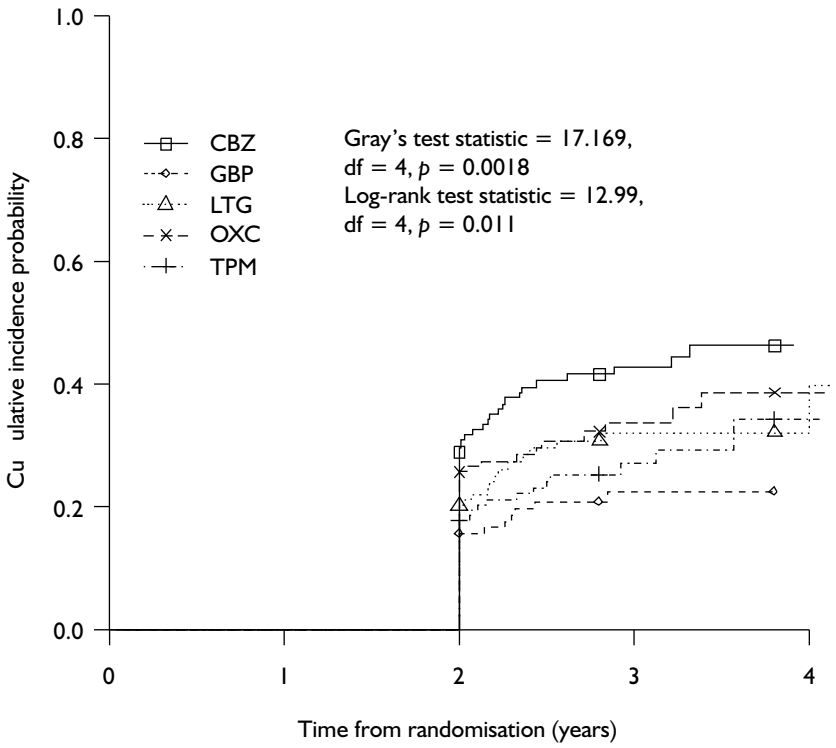


Drug (events/ total)		Year		
		2	3	4
CBZ (81/206)	Number at risk	145	34	5
	% 24-month remission (95% CI)	34 (27 to 42)	56 (47 to 65)	63 (53 to 72)
OXC (68/200)	Number at risk	138	39	5
	Difference in % 24-month remission compared with CBZ (95% CI)	–4 (–15 to 7)	–6 (–19 to 6)	0 (–18 to 17)

HR[a] (95% CI)	Baseline drug				
	CBZ	GBP	LTG	OXC	TPM
OXC	0.82 (0.60 to 1.14)	*1.51 (1.05 to 2.18)*	1.15 (0.81 to 1.62)	–	1.20 (0.84 to 1.70)

[a] HR > 1 indicates that 24-month remission occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 17 *Time to 24-month remission (Arm A) for recruitment after June 2001*

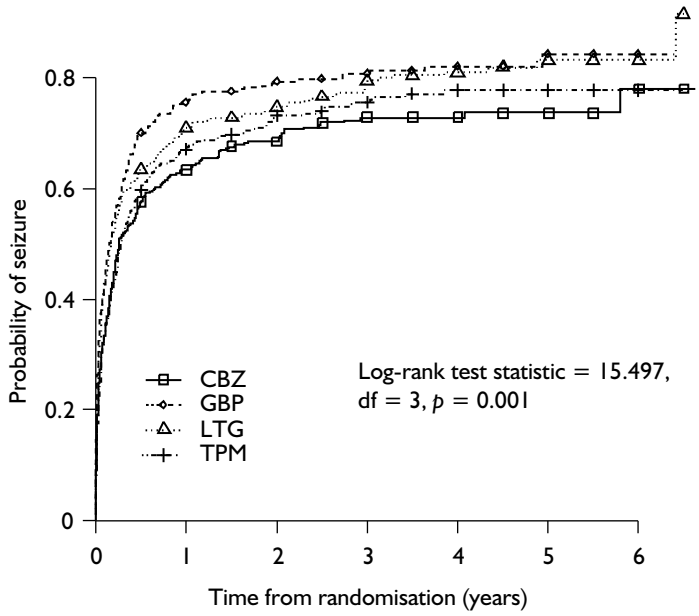


Drug (events/ total)		Year	
		2	3
CBZ (56/200)	Number at risk	78	11
	% 24-month remission (95% CI)	29 (21 to 36)	43 (34 to 51)
OXC (40/195)	Number at risk	73	14
	Difference in % 24-month remission compared with CBZ (95% CI)	–3 (–14 to 7)	–9 (–21 to 3)

HR[a] (95% CI)	Baseline drug				
	CBZ	GBP	LTG	OXC	TPM
OXC	0.74 (0.52 to 1.05)	*1.67 (1.07 to 2.63)*	1.12 (0.75 to 1.67)	–	1.26 (0.84 to 1.90)

[a] HR > 1 indicates that 24-month remission occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 18 *Time to 24-month remission (Arm A) for recruitment after June 2001 as PP analysis*

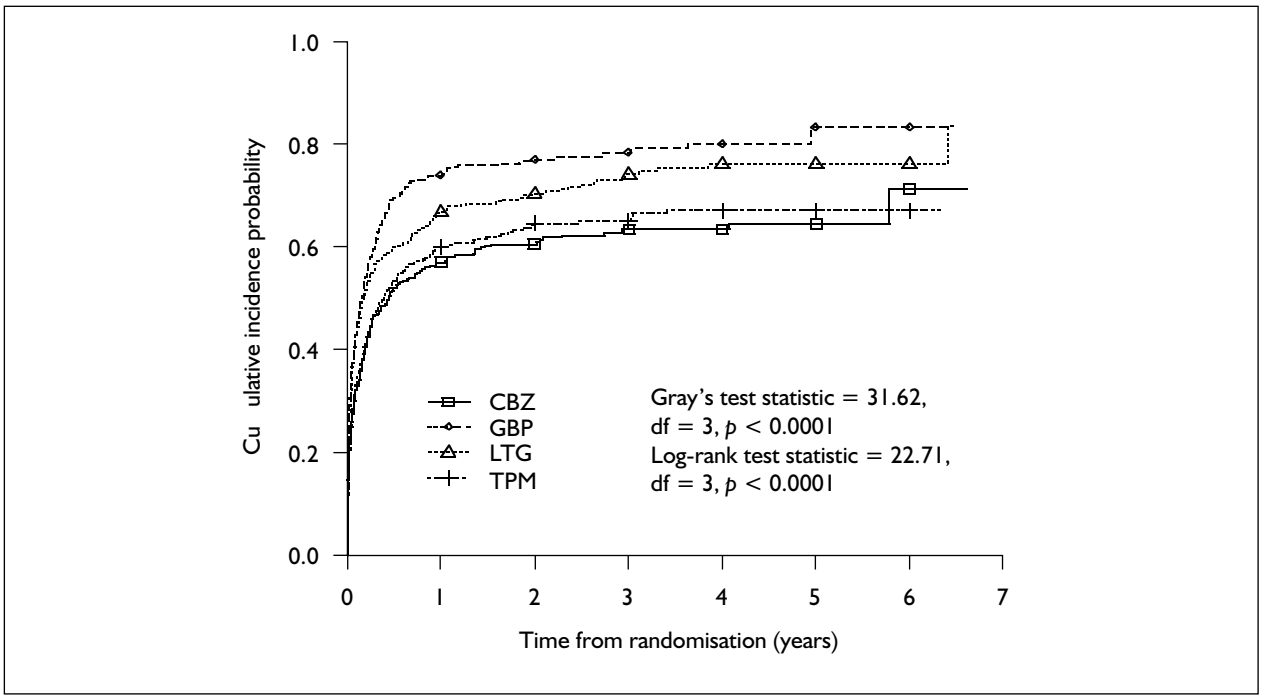


Drug (events/ total)		Year					
		1	2	3	4	5	6
CBZ (259/362)	Number at risk	126	92	53	34	17	4
	% first seizure (95% CI)	63 (58 to 68)	69 (64 to 73)	73 (68 to 78)	73 (68 to 78)	74 (69 to 79)	78 (69 to 87)
GBP (288/359)	Number at risk	83	53	39	18	7	1
	Difference in % first seizure compared with CBZ (95% CI)	12 (5 to 19)	11 (4 to 17)	8 (1 to 14)	9 (3 to 16)	11 (3 to 18)	6 (–4 to 17)
LTG (290/365)	Number at risk	106	76	48	29	10	5
	Difference in % first seizure compared with CBZ (95% CI)	7 (1 to 14)	6 (0 to 13)	7 (0 to 13)	8 (2 to 15)	10 (3 to 17)	5 (–5 to 15)
TPM (268/358)	Number at risk	112	76	50	33	13	4
	Difference in % first seizure compared with CBZ (95% CI)	4 (–3 to 11)	5 (–2 to 11)	3 (–4 to 9)	5 (–2 to 12)	4 (–3 to 11)	0 (–10 to 10)

HR[a] (95% CI)	Baseline drug			
	CBZ	GBP	LTG	TPM
CBZ	–	*0.74 (0.63 to 0.88)*	*0.82 (0.69 to 0.97)*	0.95 (0.80 to 1.13)
GBP	*1.35 (1.14 to 1.60)*	–	1.10 (0.94 to 1.30)	*1.28 (1.09 to 1.51)*
LTG	*1.23 (1.04 to 1.45)*	0.91 (0.77 to 1.07)	–	1.16 (0.99 to 1.37)
TPM	1.05 (0.89 to 1.25)	*0.78 (0.66 to 0.92)*	0.86 (0.73 to 1.02)	–

[a] HR > 1 indicates that first seizure occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 19 *Time to first seizure (Arm A) for entire recruitment period*

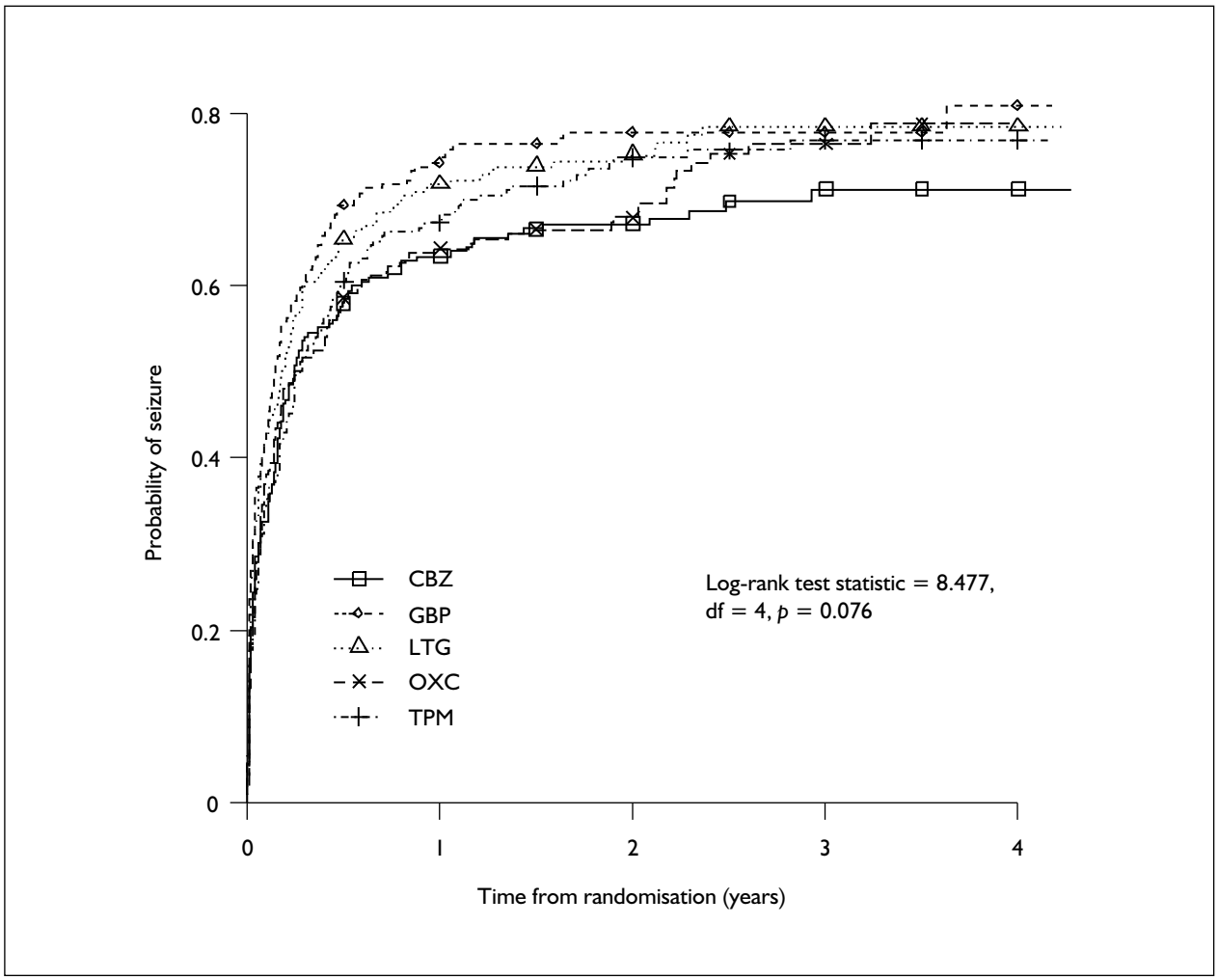


Drug (events/ total)		Year					
		1	2	3	4	5	6
CBZ (219/352)	Number at risk	95	65	35	20	8	2
	% first seizure (95% CI)	57 (52 to 62)	61 (55 to 66)	63 (58 to 69)	63 (58 to 69)	65 (59 to 70)	71 (57 to 85)
GBP (273/351)	Number at risk	64	39	26	11	3	1
	Difference in % first seizure compared with CBZ (95% CI)	17 (10 to 24)	16 (9 to 23)	15 (8 to 22)	16 (9 to 23)	19 (9 to 28)	12 (–4 to 28)
LTG (261/358)	Number at risk	85	54	32	19	9	4
	Difference in % first seizure compared with CBZ (95% CI)	10 (3 to 17)	10 (3 to 17)	11 (4 to 18)	13 (5 to 20)	12 (4 to 19)	5 (–10 to 20)
TPM (228/353)	Number at risk	81	48	29	20	8	2
	Difference in % first seizure compared with CBZ (95% CI)	3 (–4 to 10)	4 (–3 to 11)	2 (–6 to 9)	4 (–4 to 11)	3 (–5 to 10)	–4 (–19 to 11)

HR[a] (95% CI)	Baseline drug			
	CBZ	GBP	LTG	TPM
CBZ	–	*0.65 (0.54 to 0.77)*	*0.75 (0.63 to 0.90)*	0.95 (0.79 to 1.14)
GBP	*1.54 (1.29 to 1.84)*	–	1.16 (0.98 to 1.38)	*1.47 (1.24 to 1.75)*
LTG	*1.33 (1.11 to 1.59)*	0.86 (0.73 to 1.02)	–	*1.27 (1.06 to 1.51)*
TPM	1.05 (0.87 to 1.26)	*0.68 (0.57 to 0.81)*		–

[a] HR > 1 indicates that first seizure occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 20 *Time to first seizure (Arm A) for entire recruitment period as PP analysis*

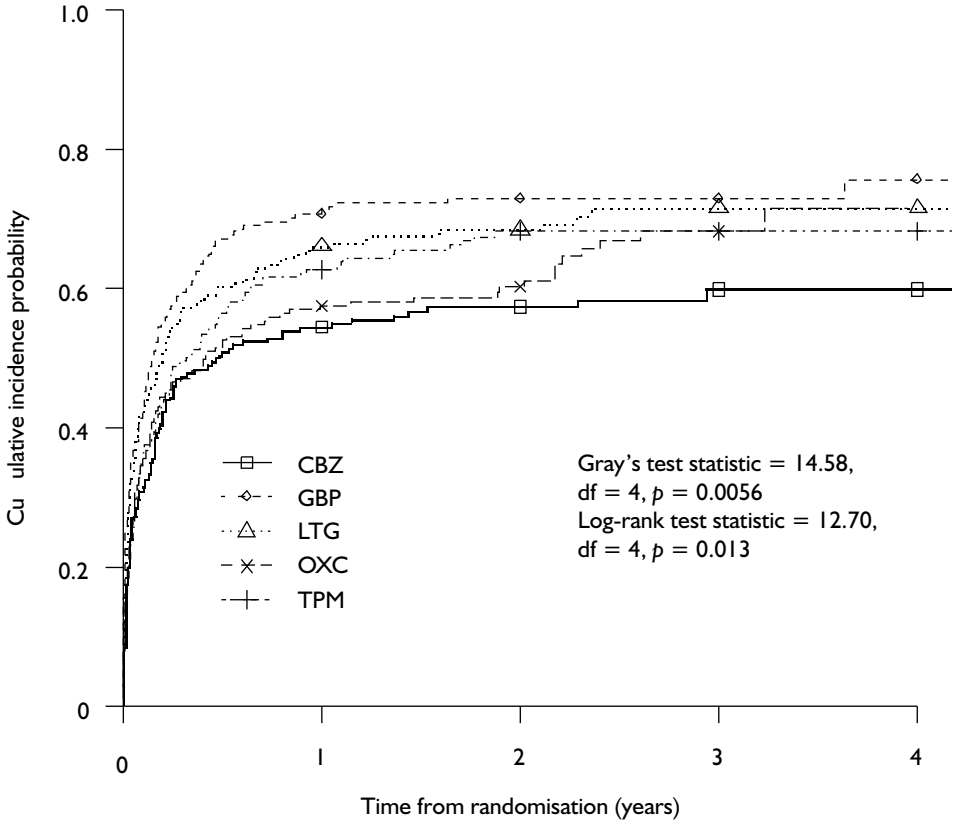


Drug (events/ total)		Year			
		1	2	3	4
CBZ (141/206)	Number at risk	71	49	19	3
	% first seizure (95% CI)	63 (57 to 70)	67 (61 to 74)	71 (64 to 78)	71 (64 to 78)
OXC (144/200)	Number at risk	67	42	11	–
	Difference in % first seizure compared with CBZ (95% CI)	1 (–8 to 10)	1 (–8 to 10)	5 (–4 to 15)	–

HR[a] (95% CI)	Baseline drug				
	CBZ	GBP	LTG	OXC	TPM
OXC	1.06 (0.84 to 1.33)	*0.79 (0.63 to 1.00)*	0.85 (0.68 to 1.06)	–	0.97 (0.77 to 1.22)

[a] HR > 1 indicates that first seizure occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 21 *Time to first seizure (Arm A) for recruitment after June 2001*



Drug (events/ total)		Year			
		1	2	3	4
CBZ (116/200)	Number at risk	58	38	16	2
	% first seizure (95% CI)	55 (48 to 61)	57 (51 to 64)	60 (53 to 67)	60 (53 to 67)
OXC (122/195)	Number at risk	51	31	6	–
	Difference in % first seizure compared with CBZ (95% CI)	3 (–7 to 13)	3 (–7 to 13)	8 (–2 to 19)	–

HR[a] (95% CI)	Baseline drug				
	CBZ	GBP	LTG	OXC	TPM
OXC	1.11 (0.86 to 1.43)	*0.73 (0.58 to 0.93)*	0.81 (0.64 to 1.03)	–	0.93 (0.73 to 1.17)

[a] HR > 1 indicates that first seizure occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 22 *Time to first seizure (Arm A) for recruitment after June 2001 as PP analysis*

CI) 1.25 (1.00 to 1.56)] whereas the older age group (65 years or older) are significantly less likely to [HR (95% CI) 0.72 (0.55 to 0.94)] compared with the middle age group (16–65 years). On adding age–treatment interaction terms, the change in –2log*L* is 3.57 (6 df, $p = 0.73$), suggesting that the pattern of treatment failure with age is not significantly different across the different drug treatment groups.

For 12-month remission, adding age as an effect results in a change in –2log*L* of 24.93 (2 df, $p < 0.0001$), suggesting that children (age < 16 years) and the older age group (65 years or more) have a significantly better chance of 12-month remission than the middle age group (16–65 years), with an HR (95% CI) of 1.22 (1.01 to 1.48) and 1.70 (1.39 to 2.09), respectively. On adding age–treatment interaction terms, the change in –2log*L* is 1.45 (6 df, $p = 0.963$), suggesting that the pattern of 12-month remission with age does not differ significantly across drug treatment groups. Consistent with this, for 24-month remission, on adding age as an effect the change in –2log*L* is 12.959 (2 df, $p = 0.0015$), with results suggesting that the probability for children (age < 16 years) does not differ significantly from the middle age group (16–65 years) [HR (95% CI) 1.09 (0.85 to 1.39)] whereas the older age group (65 years or more) has a significantly higher probability of 24-month remission than the middle age group (16–65 years) with an HR (95% CI) of 1.64 (1.28 to 2.11). On adding age–treatment interaction terms, the change in –2log*L* is 6.283 (6 df, $p = 0.39$), suggesting that the pattern of 24-month remission with age group does not differ significantly across treatment groups.

For time to first seizure, adding age has a significant overall effect, with a change in –2log*L* of 26.57 (2 df, $p < 0.0001$), with results suggesting that risk of first seizure for children (age <16 years) does not differ significantly from the middle age group (16–65 years) [HR (95% CI) 1.01 (0.84 to 1.22)] whereas the older age group (65 years or more) have a significantly lower risk of seizure than the middle age group (16–65 years), with an HR (95% CI) of 0.59 (0.47 to 0.73). On adding age–treatment interaction terms, the change in –2log*L* is 3.01 (6 df, $p = 0.81$), suggesting that the pattern of first seizure with age group does not differ significantly across drug treatment groups.

Adverse events

During follow-up, clinicians recorded adverse events described by patients on follow-up forms and indicated whether they judged them clinically important. Adverse events described were further coded in the trial office according to the scheme outlined in Appendix 1. *Table 16* summarises ITT rates of adverse events considered clinically important. An ITT approach summarises adverse events associated with the randomised policy, but as patients may have had their treatment changed during follow-up, an ITT approach does not clearly present adverse events attributable to specific drugs. *Table 17*, therefore, presents a PP summary of adverse events. *Table 18* summarises adverse events that were present close to the point of treatment failure with each drug. In each table, individual symptoms have been sorted by order of frequency of reporting.

It is notable that approximately 50% of patients reported adverse events at some point in the study and that the differences between drugs were not great. For the ITT population, LTG was the drug with the least number of patients reporting adverse events (45% ITT, 37% PP) with TPM the most (53% ITT, 49% PP).

For the individual symptoms reported, tiredness and fatigue were the most common, although these did not appear specific for any individual drug. Headache was similar. Depression, memory disturbance and a wide variety of psychiatric symptoms were common and particularly associated with TPM. Rash was a common non-central nervous system symptom, most particularly with CBZ and OXC. Rash rates were lower with LTG. GBP's particular adverse event profile was characterised by a relatively high incidence of dizziness and ataxia and weight gain, and TPM by psychiatric symptoms, including anxiety, weight loss and paraesthesia. The profiles of LTG and OXC were more non-specific. These profiles were consistent across ITT and PP summaries.

The adverse event associated with treatment failure was most commonly rash, with CBZ and OXC most commonly implicated. Again LTG was associated with a lower rate of rash leading to treatment failure. It should be noted that in the study neither patients nor clinicians were blind to drug treatment so that this may have influenced the symptoms reported to the clinicians and their assessment of the clinical importance.

QoL outcomes

Figure 23 presents information about the numbers of adult patients eligible for and responding to

TABLE 16 *Arm A – frequency of clinically important adverse events (sorted by total frequency)*[a]

	CBZ	GBP	LTG	OXC	TPM	Total
Number randomised	378	377	378	210	378	1721
Total number (%) of patients with at least one adverse event	183 (48%)	178 (47%)	169 (45%)	100 (48%)	200 (53%)	830 (48%)
Total number of adverse events experienced once or more by a patient (sum of values in bold)	396	455	376	216	495	1938
Total number of adverse event episodes (sum of values not in bold)	515	558	458	254	646	2431
Tiredness/drowsiness/fatigue/lethargy	**48** 63	**46** 62	**31** 42	**22** 27	**43** 54	**190** 248
Depression	**14** 21	**18** 24	**20** 31	**7** 8	**29** 45	**88** 129
Headache	**21** 30	**20** 27	**21** 29	**9** 10	**17** 31	**88** 127
Allergic rash	**38** 43	**13** 15	**17** 21	**20** 24	**17** 23	**105** 126
Memory problems	**20** 28	**22** 32	**13** 14	**13** 14	**26** 37	**94** 125
Dizziness/vertigo	**14** 19	**23** 28	**15** 21	**13** 14	**15** 26	**80** 108
Other psychiatric	**16** 18	**17** 19	**11** 12	**7** 8	**37** 46	**88** 103
Worsening of seizures	**17** 24	**22** 31	**17** 21	**3** 3	**17** 20	**76** 99
Other neurological	**9** 18	**21** 25	**15** 18	**8** 8	**18** 22	**71** 91
Other general	**13** 17	**19** 19	**19** 24	**9** 10	**16** 20	**76** 90
Behaviour/personality change/aggression	**12** 17	**9** 11	**12** 16	**2** 4	**24** 34	**59** 82
Ataxia	**9** 12	**24** 28	**14** 16	**8** 11	**9** 12	**64** 79
Confusion/difficulty thinking/disoriented	**9** 11	**16** 17	**8** 9	**8** 9	**22** 26	**63** 72
Anxiety/agitation/nervousness	**7** 7	**15** 15	**8** 8	**7** 8	**15** 21	**52** 59
Weight loss	**2** 3	**4** 6	**4** 4	**3** 3	**29** 37	**42** 53
Diplopia	**5** 7	**11** 17	**4** 5	**8** 14	**6** 6	**34** 49
Nausea	**9** 11	**7** 7	**9** 9	**15** 16	**4** 5	**44** 48
Weight gain	**9** 13	**15** 21	**4** 4	**1** 1	**5** 8	**34** 47
Accidental injury	**7** 7	**11** 13	**12** 14	**3** 3	**8** 8	**41** 45
Pins and needles/dysaesthesia	**4** 5	**5** 6	**3** 3	**0** 0	**26** 31	**38** 45
Sleep disturbance	**5** 7	**4** 4	**9** 9	**4** 9	**9** 13	**31** 42
Other[b]	**108** 134	**113** 131	**110** 128	**46** 50	**103** 121	**480** 564

[a] Values in bold represent the number of patients who have reported a specific side-effect. Other values represent the number of reported occurrences of a specific side-effect.

[b] Sorted by descending total frequency: other cardiac/vascular; other skin and appendages; abdominal pain, dyspepsia; other gastrointestinal; other visual disturbance; other renal tract/genital; diarrhoea; tremor; aches and pains; constipation; infection; mouth/gum problem; other respiratory/pulmonary; ischaemic heart disease/myocardial infarct; other haematological; other musculoskeletal; vomiting; impotence/libido problems; allopecia; word finding difficulty; status epilepticus; stroke – infarction; diabetes mellitus; hearing problem/tinnitus; hypertension; anorexia; bruising; flu-like symptoms; haemorrhage; malignancy; short of breath; vaginal bleeding; arthritis; eczema; peptic ulceration; asthma; other hepatobiliary; urinary retention; abnormal liver function tests; anaemia; childbirth; myalgia; other endocrine; psoriasis; upper respiratory tract infection (URTI), catarrh, sinusitis, rhinorrhoea; urinary tract infection (UTI); faints; hallucinations; hepatitis; pancreatitis; psychosis; transient ischaemic attacks (TIAs); tachycardia; thyroid disease; venous thrombosis.

the QoL study at baseline and at 2-year follow-up. In all, 1881 adults were eligible, 1453 in Arm A and 428 in Arm B of the trial. A total of 1587 adults responded at baseline (rate of 84.4%) and 294 did not (reasons for non-response are shown in the relevant box in *Figure 23*); 1058 responded at 2 years (rate of 71%) and 426 did not (reasons are shown in the relevant box). Comparison of responders and non-responders to the baseline and 2-year follow-up assessments revealed that there were some important differences between them, with potential to create bias in the interpretation of the results of the QoL study. These comparisons are presented in full in Appendix 7 and we draw attention to them here and the consequent need for caution in considering the results.

A total of 1453 adults sent baseline QoL questionnaires were randomised into the CBZ arm. Response rates in this arm of the trial are presented in *Tables 19* and *20*. (In *Tables 19* and *20*, the analyses exclude the 108 individuals in Arm A whose 2-year QoL assessment was

TABLE 17 *Arm A – frequency of clinically important adverse events (sorted by total frequency) as per protocol (adverse events experienced up to withdrawal of drug or last follow-up for PP population)*[a]

	CBZ	GBP	LTG	OXC	TPM	Total
Number randomised	358	358	363	197	358	1634
Total number (%) of patients with at least one adverse event	144 (40%)	143 (40%)	133 (37%)	88 (45%)	175 (49%)	683 (42%)
Total number of adverse events experienced once or more by a patient (sum of values in bold)	249	293	241	160	356	1299
Total number of adverse events (sum of values not in bold)	327	337	281	187	456	1588
Tiredness/drowsiness/fatigue/lethargy	**36** 45	**34** 40	**17** 22	**16** 19	**33** 43	**136** 169
Memory problems	**12** 19	**19** 23	**10** 10	**8** 9	**19** 29	**68** 90
Allergic rash	**32** 34	**4** 4	**15** 18	**16** 20	**8** 11	**75** 87
Depression	**8** 11	**10** 12	**13** 16	**5** 6	**24** 33	**60** 78
Headache	**9** 15	**15** 19	**13** 18	**6** 6	**11** 16	**54** 74
Other psychiatric	**7** 8	**9** 11	**7** 7	**5** 6	**31** 39	**59** 71
Dizziness/vertigo	**10** 14	**15** 16	**9** 9	**12** 13	**8** 9	**54** 61
Confusion/difficulty thinking/disoriented	**9** 11	**15** 16	**4** 4	**6** 7	**19** 22	**53** 60
Other neurological	**6** 14	**14** 16	**9** 9	**5** 5	**12** 16	**46** 60
Other general	**6** 7	**11** 11	**13** 17	**6** 7	**12** 14	**48** 56
Behaviour/personality change/aggression	**4** 6	**6** 6	**7** 10	**1** 2	**19** 29	**37** 53
Worsening of seizures	**5** 6	**13** 15	**12** 16	**1** 1	**8** 10	**39** 48
Anxiety/agitation/nervousness	**7** 7	**11** 11	**5** 5	**6** 7	**12** 15	**41** 45
Ataxia	**6** 9	**12** 14	**9** 9	**6** 8	**3** 4	**36** 44
Weight loss	**1** 2	**2** 3	**2** 2	**1** 1	**27** 35	**33** 43
Nausea	**6** 7	**3** 3	**6** 6	**13** 14	**4** 5	**32** 35
Weight gain	**7** 10	**12** 17	**1** 1	**0** 0	**4** 5	**24** 33
Pins and needles/dysaesthesia	**1** 1	**1** 1	**1** 1	**0** 0	**24** 29	**27** 32
Sleep disturbance	**2** 4	**4** 4	**8** 8	**2** 5	**8** 11	**24** 32
Other[b]	**75** 97	**83** 95	**80** 93	**45** 51	**70** 81	**353** 417

[a] Values in bold represent the number of patients who have reported a specific side-effect. Other values represent the number of reported occurrences of a specific side-effect.

[b] Sorted by descending total frequency: other cardiac/vascular; accidental injury; diplopia; other skin and appendages; other visual disturbance; abdominal pain, dyspepsia; diarrhoea; other gastrointestinal; other renal tract/genital; aches and pains; mouth/gum problem; tremor; constipation; infection; other musculoskeletal; other respiratory/pulmonary; other haematological; allopecia; impotence/libido problems; ischaemic heart disease/myocardial infarct; vomiting; stroke–infarction; word finding difficulty; vaginal bleeding; bruising; haemorrhage; malignancy; short of breath; status epilepticus; asthma; diabetes mellitus; eczema; flu-like symptoms; hearing problem/tinnitus; hypertension; urinary retention; anorexia; other endocrine; other hepatobiliary; psoriasis; URTI, catarrh, sinusitis, rhinorrhoea; anaemia; arthritis; childbirth; faints; myalgia; peptic ulceration; TIAs; tachycardia; thyroid disease; venous thrombosis.

pending/not due, or who had emigrated or experienced a non-epilepsy death.) *Table 19* presents data for participants randomised into the trial across the whole time period, but excludes those randomised to OXC. *Table 20* is restricted to those participants randomised into the trial after the introduction of OXC. Differences in response by treatment group were observed for the CBZ arm only when considering the period after the inclusion of OXC; there were no significant differences when the whole time period excluding OXC was considered.

In this analysis, we present information for measures of QoL defined as **core** only (anxiety and depression; patient-perceived drug side-effects; cognitive functioning; EQ-5D; GQoL). A full QoL analysis will be presented in a separate publication. *Tables 21–28* therefore present scores (with 95% CIs) for the core QoL measures at 2 years by treatment group adjusted for baseline values. In each table, columns represent the baseline comparator: for example, in the CBZ column, scores are for the other groups **compared with** CBZ. All columns other than the OXC column are for the whole period: in the latter, scores are for

TABLE 18 *Most recent adverse event (sorted by total frequency) reported before treatment failure for UAE or UAE+ISC (Arm A) based on PP population*[a]

	CBZ	GBP	LTG	OXC	TPM	Total
Number of patients (per protocol)	358	358	363	197	358	1634
Number of treatment failures for UAE	98 (27%)	57 (16%)	60 (17%)	48 (24%)	99 (28%)	362 (22%)
Number of treatment failures for UAE and ISC	20 (6%)	32 (9%)	11 (3%)	11 (6%)	28 (8%)	102 (6%)
Clinically important						
Allergic rash	25	3	10	11	6	55
Tiredness/drowsiness/fatigue/lethargy	16	13	5	5	16	55
Headache	2	7	5	5	10	29
Other psychiatric	4	5	2	1	15	27
Dizziness/vertigo	3	6	5	7	4	25
Confusion/difficulty thinking/disoriented	4	5	1	3	11	24
Depression	0	3	4	3	12	22
Memory problems	3	8	1	2	6	20
Behaviour/personality change/aggression	3	3	2	1	10	19
Anxiety/agitation/nervousness	3	2	4	1	8	18
Ataxia	3	9	1	3	1	17
Nausea	2	2	3	8	2	17
Other neurological	2	5	2	1	5	15
Other general	1	4	3	2	5	15
Pins and needles/dysaesthesia	0	0	0	0	14	14
Weight gain	4	6	1	0	3	14
Weight loss	1	0	1	0	9	11
Diarrhoea	3	0	3	1	3	10
Sleep disturbance	0	1	5	1	3	10
Other[b]	22	16	14	19	21	92
Not known	7	5	4	2	1	19
Not clinically important						
Failure for UAE	27	17	16	10	20	90
Failure for UAE + ISC	12	9	5	1	5	32

[a] Tabulated values represent the number of patients who have reported a specific side-effect.
[b] Sorted by descending total frequency: diplopia; worsening of seizures; other skin and appendages; abdominal pain, dyspepsia; other visual disturbance; mouth/gum problem; other gastrointestinal; tremor; constipation; aches and pains; other haematological; vomiting; allopecia; impotence/libido problems; other renal tract/genital; accidental injury; other respiratory/pulmonary; word finding difficulty; eczema; anorexia; bruising; faints; flu-like symptoms; malignancy; myalgia; other cardiac/vascular; other endocrine; vaginal bleeding.

TABLE 19 *QoL study response rates in Arm A across the whole period (excluding OXC)*

	CBZ (%)	GBP (%)	LTG (%)	TPM (%)	*p*-Value
No. sent a baseline questionnaire	304	300	288	295	
No. returning a baseline questionnaire	262 (86)	260 (87)	241 (84)	240 (81)	0.250
No. returning a 2-year questionnaire	196 (64)	201 (67)	181 (63)	174 (59)	0.227
No. returning a baseline and a 2-year questionnaire	195 (64)	197 (66)	177 (61)	172 (58)	0.264

the other groups compared with OXC for the period after the inclusion of OXC only. Values for continuous measures are the coefficients from a multiple regression representing the difference between treatments, with 95% CIs. Values for ordinal measures are the exponentiated coefficients from a proportional odds model, with 95% CIs, such that the values represent the odds of increasing severity of outcome.

For Arm A, few statistically significant differences in QoL between treatment groups were identified, although some trends in the data with regard to direction of treatment effects were evident. Thus,

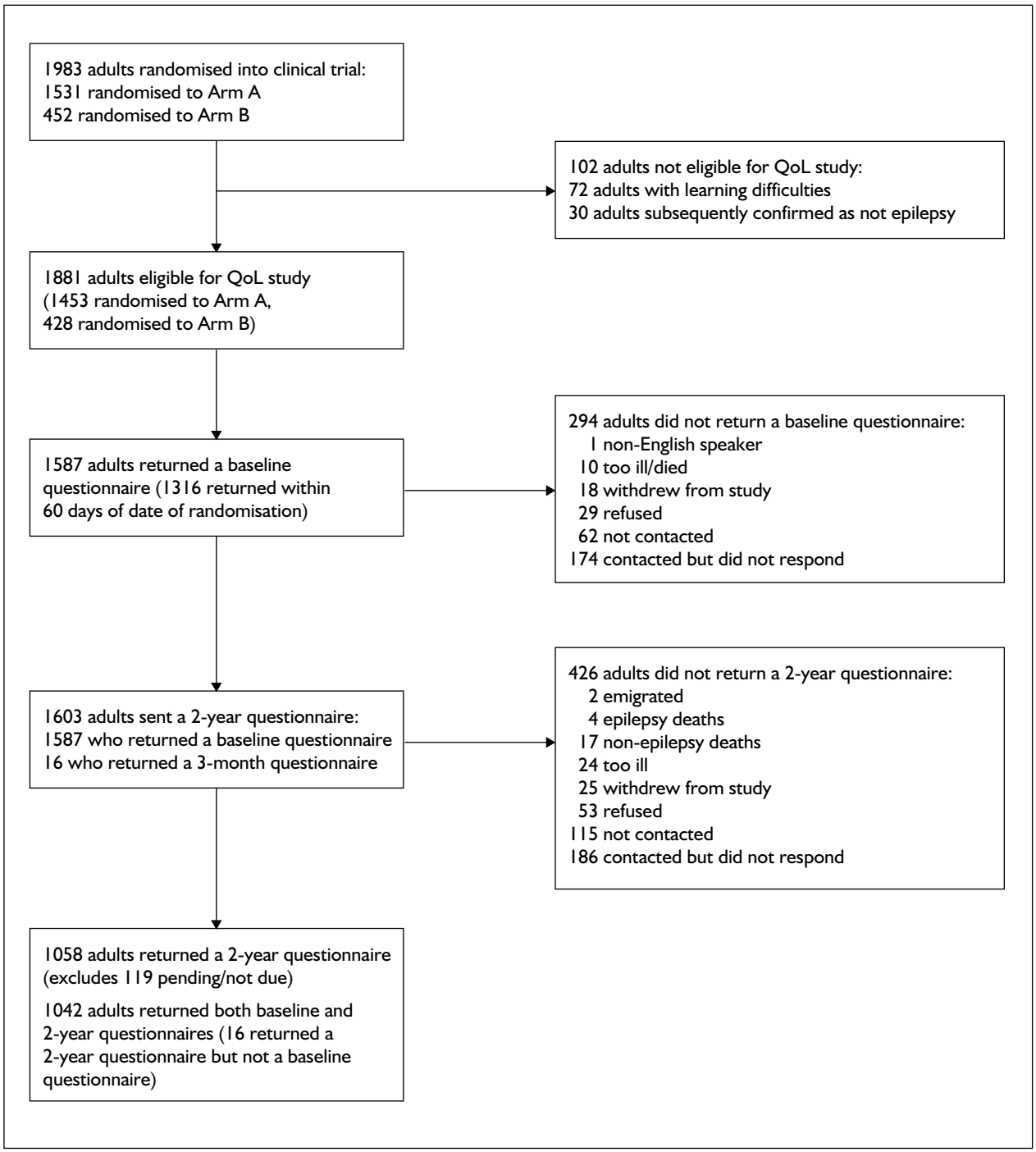


FIGURE 23 *Flow chart for adult participants in QoL analyses*

TABLE 20 *QoL study response rates in Arm A for the period after the introduction of OXC*

	CBZ (%)	GBP (%)	LTG (%)	TPM (%)	OXC (%)	*p*-Value
No. sent a baseline questionnaire	163	167	160	159	158	
No. returning a baseline questionnaire	141 (87)	145 (87)	130 (81)	124 (78)	130 (82)	0.172
No. returning a 2-year questionnaire	107 (66)	123 (74)	95 (59)	91 (57)	94 (59)	0.013
No. returning a baseline and 2-year questionnaire	107 (66)	121 (72)	92 (58)	90 (57)	92 (58)	0.011

TABLE 21 *Two-year anxiety scores*

	CBZ	GBP	LTG	TPM	OXC
CBZ	–	0.01 (–0.76 to 0.78)	0.09 (–0.70 to 0.88)	0.84 (0.04 to 1.63)	–0.13 (–1.10 to 0.83)
GBP	–0.01 (–0.78 to 0.76)	–	0.08 (–0.71 to 0.87)	0.83 (0.03 to 1.62)	–0.15 (–1.11 to 0.81)
LTG	–0.09 (–0.88 to 0.70)	–0.08 (–0.87 to 0.71)	–	0.75 (–0.07 to 1.56)	–0.23 (–1.21 to 0.76)
TPM	–0.84 (–1.63 to –0.04)	–0.83 (–1.62 to –0.03)	–0.75 (–1.56 to 0.07)	–	–0.97 (–1.96 to 0.01)

TABLE 22 *Two-year depression scores*

	CBZ	GBP	LTG	TPM	OXC
CBZ	–	–0.28 (–0.94 to 0.37)	0.35 (–0.33 to 1.02)	–0.09 (–0.77 to 0.59)	–0.29 (–1.11 to 0.53)
GBP	0.28 (–0.37 to 0.94)	–	0.63 (–0.04 to 1.30)	0.19 (–0.48 to 0.86)	–0.01 (–0.82 to 0.81)
LTG	–0.35 (–1.02 to 0.33)	–0.63 (–1.30 to 0.04)	–	–0.44 (–1.13 to 0.25)	–0.63 (–1.47 to 0.20)
TPM	0.09 (–0.59 to 0.77)	–0.19 (–0.86 to 0.48)	0.44 (–0.25 to 1.12)	–	–0.20 (–1.04 to 0.64)

TABLE 23 *Two-year AEP scores*

	CBZ	GBP	LTG	TPM	OXC
CBZ	–	–0.60 (–2.34 to 1.15)	–0.47 (–2.32 to 1.38)	0.60 (–1.23 to 2.42)	0.45 (–1.83 to 2.72)
GBP	0.60 (–1.15 to 2.34)	–	0.13 (–1.72 to 1.97)	1.19 (–0.62 to 3.01)	1.04 (–1.23 to 3.32)
LTG	0.47 (–1.38 to 2.32)	–0.13 (–1.97 to 1.72)	–	1.07 (–0.85 to 2.99)	0.91 (–1.44 to 3.26)
TPM	–0.60 (–2.42 to 1.23)	–1.19 (–3.01 to 0.62)	–1.07 (–2.99 to 0.85)	–	–0.15 (–2.48 to 2.19)

TABLE 24 *Two-year neurotoxicity scale scores*

	CBZ	GBP	LTG	TPM	OXC
CBZ	–	0.12 (–2.63 to 2.86)	1.30 (–1.57 to 3.93)	1.58 (–1.27 to 4.42)	–0.72 (–4.12 to 2.68)
GBP	–0.12 (–2.86 to 2.63)	–	1.18 (–1.57 to 3.93)	1.48 (–1.32 to 4.28)	–0.79 (–4.15 to 2.57)
LTG	–1.30 (–4.09 to 1.50)	–1.18 (–3.93 to 1.57)	–	0.30 (–2.54 to 3.14)	–1.98 (–5.38 to 1.42)
TPM	–1.60 (–4.43 to 1.24)	–1.48 (–4.28 to 1.32)	–0.30 (–3.14 to 2.54)	–	–2.29 (–5.73 to 1.15)

TABLE 25 *Two-year EQ-5D scores*

	CBZ	GBP	LTG	TPM	OXC
CBZ	–	–0.01 (–0.06 to 0.04)	–0.02 (–0.06 to 0.03)	–0.03 (–0.08 to 0.02)	0.01 (–0.05 to 0.07)
GBP	0.01 (–0.04 to 0.06)	–	–0.01 (–0.05 to 0.04)	–0.02 (–0.07 to 0.03)	0.02 (–0.04 to 0.08)
LTG	0.02 (–0.03 to 0.06)	0.01 (–0.04 to 0.05)	–	–0.01 (–0.06 to 0.04)	0.03 (–0.03 to 0.08)
TPM	0.03 (–0.02 to 0.08)	0.02 (–0.03 to 0.07)	0.01 (–0.04 to 0.06)	–	0.04 (–0.02 to 0.10)

TABLE 26 *Two-year anxiety scores – ordinal*

	CBZ	GBP	LTG	TPM	OXC
CBZ	–	0.98 (0.63 to 1.53)	1.04 (0.66 to 1.65)	1.60 (1.01 to 2.60)	1.02 (0.58 to 1.79)
GBP	1.02 (0.65 to 1.59)	–	1.06 (0.67 to 1.68)	1.65 (1.03 to 2.65)	1.03 (0.59 to 1.82)
LTG	0.96 (0.61 to 1.52)	0.94 (0.60 to 1.49)	–	1.55 (0.96 to 2.53)	0.98 (0.55 to 1.75)
TPM	0.62 (0.38 to 0.99)	0.61 (0.38 to 0.98)	0.64 (0.40 to 1.05)	–	0.64 (0.35 to 1.15)

TABLE 27 *Two-year depression scores – ordinal*

	CBZ	GBP	LTG	TPM	OXC
CBZ	–	0.75 (0.45 to 1.23)	1.34 (0.79 to 2.30)	0.88 (0.53 to 1.47)	1.13 (0.57 to 2.24)
GBP	1.34 (0.81 to 2.21)	–	1.80 (1.06 to 3.05)	1.18 (0.72 to 1.96)	1.51 (0.77 to 2.96)
LTG	0.74 (0.44 to 1.27)	0.56 (0.33 to 0.94)	–	0.66 (0.38 to 1.13)	0.84 (0.41 to 1.70)
TPM	1.13 (0.68 to 1.89)	0.85 (0.51 to 1.40)	1.52 (0.89 to 2.62)	–	1.27 (0.64 to 2.54)

TABLE 28 *Two-year GQoL scores*

	CBZ	GBP	LTG	TPM	OXC
CBZ	–	1.13 (0.78 to 1.65)	1.32 (0.90 to 1.93)	1.10 (0.74 to 1.62)	1.34 (0.84 to 2.15)
GBP	0.88 (0.61 to 1.28)	–	1.16 (0.80 to 1.69)	0.97 (0.66 to 1.42)	1.19 (0.75 to 1.89)
LTG	0.76 (0.52 to 1.12)	0.86 (0.59 to 1.26)	–	0.83 (0.56 to 1.23)	1.02 (0.64 to 1.64)
TPM	0.91 (0.62 to 1.34)	1.03 (0.70 to 1.52)	1.20 (0.81 to 1.77)	–	1.22 (0.76 to 1.97)

based both on mean scores (*Table 21*) and 'caseness' (*Table 26*), the likelihood of anxiety was statistically significantly reduced for TPM (in spite of this symptom being commonly reported to clinicians by patients taking the drug), compared with CBZ and GBP (although the size of the reduction was small and the 95% CIs relatively wide), and there was a non-significant reduction in risk for TPM compared with LTG or OXC. Likewise, based both on mean scores (*Table 22*) and 'caseness' (*Table 27*), there was a trend for reduced risk of depression for LTG compared with the other AEDs, and the difference reached statistical significance for LTG compared with GBP (although again the difference was small and the 95% CIs relatively wide). There were no important differences or trends for scores on the AEP, the Neurotoxicity Scale, the EQ-5D or for GQoL.

Given that some important differences were identified with regard to the baseline QoL profiles and clinical outcomes of responders to the QoL study compared with non-responders (see Appendix 7), the results for this analysis need to be interpreted with caution. The lack of between-treatment group differences may, in fact, reflect that those with the poorest QoL outcomes failed to return a 2-year questionnaire, so that important effects were diluted or missed. To consider the robustness of the results with respect to responder bias, hotdecked imputations were used (Appendix 6), although it is important to note that patient matching in the hotdecking did not include matching for randomised drug because the numbers were insufficient to make this possible. Bearing in mind this caveat, these imputations confirm, as might be expected, that for some comparisons the size and direction of the results may have been influenced by responder bias. Hence, although the overall conclusions are not substantially altered, some differences ceased to be statistically significant, including the finding of reduced anxiety for TPM compared with the other drugs.

QoL outcomes by achievement of a 12-month remission or withdrawal of original AED

In contrast to the marked lack of between-drug differences in 2-year QoL outcomes for Arm A, there were a number of statistically significant differences both for achieving a positive (i.e. remission of seizures) and a negative (i.e. treatment failure of the original randomised drug) clinical outcome (*Tables 29* and *30*). For each, effects are expressed as regression coefficients or exponentiated coefficients. All comparisons achieved statistical significance, with the direction of effects showing better QoL for those who achieved remission or had not been withdrawn from the randomised drug.

Thus, achieving a 12-month remission of seizures by 2-year follow-up was associated with a decreased risk of anxiety and depression (measured both by mean scores and caseness), a decreased risk of cognitive (neurotoxicity) and other AED adverse effects, and a reduced likelihood of scoring negatively for GQoL (*Table 29*). There was also a small but significant improvement for QoL as measured by scores on the EQ-5D. Withdrawing from the randomised

TABLE 29 *ARM A – QoL measures by whether a 12-month remission was achieved (effects represent the regression coefficients for the effect of achieving remission)*

QoL measure	Effect	Estimate (95% CI)
Anxiety	Difference	–1.80 (–2.33 to –1.27)
Depression	Difference	–1.40 (–1.85 to –0.95)
ABNAS	Difference	–6.35 (–8.26 to –4.45)
AEP	Difference	–3.48 (–4.75 to –2.21)
EQ-5D	Difference	0.07 (0.04 to 0.10)
Anxiety	Odds ratio	0.47 (0.35 to 0.64)
Depression	Odds ratio	0.42 (0.29 to 0.59)
GQoL	Odds ratio	0.44 (0.34 to 0.58)

TABLE 30 *ARM A – QoL measures by withdrawal of drug by 2-year follow-up (effects represent the regression coefficients for the effect of being withdrawn)*

QoL measure	Effect	Estimate (95% CI)
Anxiety	Difference	1.30 (0.76 to 1.83)
Depression	Difference	0.95 (0.49 to 1.40)
ABNAS	Difference	4.28 (2.34 to 6.22)
AEP	Difference	3.02 (1.77 to 4.26)
EQ-5D	Difference	–0.03 (–0.06 to –0.00)
Anxiety	Odds ratio	1.97 (1.45 to 2.69)
Depression	Odds ratio	1.91 (1.34 to 2.71)
GQoL	Odds ratio	1.55 (1.19 to 2.02)

drug by 2-year follow-up was associated with increased risk of anxiety and depression, increased risk of cognitive and other AED adverse effects, poorer QoL as measured by EQ-5D score and an increased likelihood of scoring negatively for GQoL (*Table 30*).

In trying to determine a meaningful difference in QoL measures between treatment groups, the observed differences between those achieving and those failing to achieve a 12-month remission may be considered a useful benchmark. Wiebe and colleagues[67] used a 'reliability change index' to obtain threshold values for change beyond chance or measurement error for a range of epilepsy-specific QoL scales. They reported that for one measure used in the SANAD trial, the AEP, score changes of the dimensions noted here would not reflect real change. It is worthy of note, however, that in their study Wiebe and colleagues[67] were concerned with QoL assessments made in patients with intractable epilepsy awaiting surgery, for whom the tolerability threshold for AED side-effects may be considerably greater. Furthermore, Wiebe and colleagues conceded that threshold values for real change should not be seen as indicators of, or surrogates for, minimum clinically important change, the latter likely to be substantially smaller than the threshold value.

Health economic outcomes

Cost per QALY analysis

Tests of differences in baseline EQ-5D values between the groups were performed, with no statistically significant differences being found.

CBZ, GBP, LTG, TPM

This analysis is based on 636 adult patients who provided complete EQ-5D responses. The numbers of patients in each drug group are CBZ = 170, GBP = 173, LTG = 143 and TPM = 150.

Table 31 shows the breakdown of hospitalisation resource use and 'other' resource use among patients when OXC is excluded.

Table 32 shows the contribution of AED costs, hospitalisation costs and 'other' costs to the average cost per patient.

Table 33 shows the point estimates of the ICERs for the new AEDs. These ICERs are estimated

ABLE 31 *Breakdown of resource use (O C excluded)*

Item of resource use	Number of patients reporting contact	verage number of contacts among patients reporting contact (95% CI)			
Hospitalisations					
ICU					
sychiatric ward					
Medical ward	7.3 (–6.0 to 20.6)	2.7 (–2.5 to 7.8)	7.4 (1.1 to 13.8)	14.4 (–5.1 to 33.8)	
Surgical ward	7 (–6.8 to 20.8)	7.3 (–3.0 to 17.7)	2.4 (0.5 to 4.3)	7.0 (0.9 to 13.0)	
				1.2 (0.6 to 1.8)	
Other				2.7 (–2.5 to 7.8)	
Other					
Nurse at GP surgery	7.6 (5.5 to 9.8)	9.8 (5.0 to 14.5)	6.2 (4.6 to 7.8)	6.1 (4.4 to 7.8)	
GP at surgery	9.9 (7.7 to 12.1)	8.9 (6.7 to 11.1)	8.3 (6.3 to 10.3)	6.8 (5.8 to 7.9)	
Nurse at home	2.3 (1.5 to 3.1)	3.9 (1.6 to 6.2)	3.6 (2.2 to 5.0)	7.5 (3.9 to 11.2)	
GP at home	3.8 (2.0 to 5.7)	4.0 (3.1 to 4.9)	2.8 (1.9 to 3.7)	3.2 (2.4 to 4.0)	
Ambulance	5.2 (2.9 to 7.5)	5.0 (3.0 to 6.9)	5.6 (1.5 to 9.7)	4.2 (3.2 to 5.2)	
Blood test	5.1 (3.6 to 6.6)	5.0 (3.6 to 6.5)	5.8 (3.9 to 7.6)	4.1 (3.4 to 4.8)	
Urine test	4.8 (2.5 to 7.2)	3.1 (2.5 to 3.8)	3.7 (2.1 to 5.2)	3.7 (2.7 to 4.7)	
Ultrasound	1.8 (0.3 to 3.2)	1.8 (0.7 to 2.8)	3.4 (1.1 to 5.6)	2.0 (0.8 to 3.2)	
-ray	3.9 (1.8 to 6.0)	2.5 (1.5 to 3.5)	3.2 (1.9 to 4.4)	5.8 (3.8 to 7.8)	
CT scan	1.9 (1.4 to 2.4)	2.8 (1.9 to 3.8)	2.0 (1.3 to 2.6)	2.3 (1.6 to 2.9)	
MRI scan	2.0 (1.5 to 2.4)	2.8 (2.1 to 3.5)	2.3 (1.8 to 2.8)	2.8 (2.1 to 3.5)	
	1.4 (1.1 to 1.7)	1.9 (1.4 to 2.4)	1.8 (1.2 to 2.4)	2.1 (1.6 to 2.6)	
Health visitor	4.4 (–0.7 to 9.6)		6.0 (0.1 to 11.9)		
Social worker	4.4 (3.0 to 5.8)	5.2 (2.6 to 7.7)	5.0 (3.9 to 6.1)	3.0 (1.4 to 4.6)	
Disablement resettlement officer	3.5 (1.6 to 5.4)			3.5 (0.3 to 6.8)	
sychologist	4.4 (2.9 to 5.9)	6.9 (1.9 to 11.9)	4.8 (1.7 to 7.9)	6.8 (2.5 to 11.0)	
Counsellor	9.8 (1.0 to 18.6)	8.3 (–0.03 to 16.6)	5.0 (2.1 to 7.9)	13.3 (1.4 to 25.3)	
Educational/vocational officer	9.0 (7.1 to 11.0)	8.3 (1.7 to 15.0)	3.3 (0.5 to 6.2)	4.7 (1.4 to 8.0)	

, computed tomography; ICU, intensive care unit; MRI, magnetic resonance imaging.

[a] esource use associated with the management of adverse events requiring hospitalisation.

[b] Other healthcare and social services resource use.

TABLE 32 *The contribution of AED costs, hospitalisation costs and 'other' costs to the average cost per patient*

AED	Average cost per patient (£) (95% CI)	Breakdown of average cost per patient (£) (95% CI)		
		AEDs	Hospitalisation[a]	Other[b]
CBZ	1226 (970 to 1482)	404 (317 to 489)	143 (–36 to 321)	679 (536 to 823)
TPM	2009 (1699 to 2319)	1123 (1010 to 1237)	166 (–1.06 to 332)	720 (535 to 906)
LTG	2257 (1948 to 2566)	1287 (1188 to 1386)	244 (49 to 440)	726 (508 to 944)
GBP	2561 (2139 to 2984)	1493 (1370 to 1617)	312 (–50 to 675)	756 (606 to 905)

[a] Costs associated with the management of adverse events requiring hospitalisation.
[b] Other healthcare and social services costs.

TABLE 33 *ICERs for the new AEDs (OXC excluded)*

AED	Cost (£) (95% CI)	QALYs (95% CI)	Incremental cost (£)	Incremental QALYs	ICER (£/QALY)
CBZ	1,226 (970 to 1482)	1.477 (1.40 to 1.56)	–	–	–
TPM	2,009 (1699 to 2319)	1.501 (1.42 to 1.58)	783	0.024	32,625 extended dominance
LTG	2,257 (1948 to 2566)	1.564 (1.48 to 1.64)	248	0.063	11,851
GBP	2,561 (2139 to 2984)	1.491 (1.40 to 1.58)	304	–0.073	Dominated

using the lowest costs for CBZ and LTG (CBZ_{low} and LTG_{low}).

GBP has a positive incremental cost and a negative incremental QALY gain and is therefore dominated by LTG. Because LTG has a lower ICER than TPM, TPM is ruled out on the grounds of extended dominance. The ICER for LTG relative to CBZ is £11,851.

The same pattern of results is found when using different combinations of high and low costs for CBZ and LTG. The lowest value of the ICER for LTG is when CBZ_{high} and LTG_{low} are used and is equal to £11,149. The highest value of the ICER for LTG is when CBZ_{low} and LTG_{high} are used and is equal to £14,042.

The results of the sensitivity analysis on the assumptions made in the AUC approach to estimating QALYs did not impact on the relative ICERs (and therefore the pattern of results). The baseline estimate of the ICER for LTG relative to CBZ (£11,851) ranged from £11,207 to £12,573 depending on the assumptions made.

Cost-effectiveness acceptability curves. Bootstrapping the baseline point estimate of the ICER for LTG relative to CBZ results in 95% of the replications being located in the NE quadrant of the cost-effectiveness plane (more costly, more effective), with the remaining 5% being located in the NW quadrant (more costly, less effective).

Figure 24 shows the CEAC for LTG relative to CBZ. The CEAC shows the probability that LTG is cost-effective for every possible value of the ceiling ratio (λ).

To provide a comparative context for the CEAC for LTG, *Figures 25* and *26* show the CEACs for GBP and TPM relative to CBZ. The probabilities that each of the new AEDs is cost-effective at ceiling ratios of £10,000, £30,000 and £50,000 per QALY are presented in *Table 34*.

CBZ, GBP, LTG, OXC, TPM

This analysis is based on 414 adult patients who provided complete EQ-5D responses. The numbers of patients in each drug group are CBZ

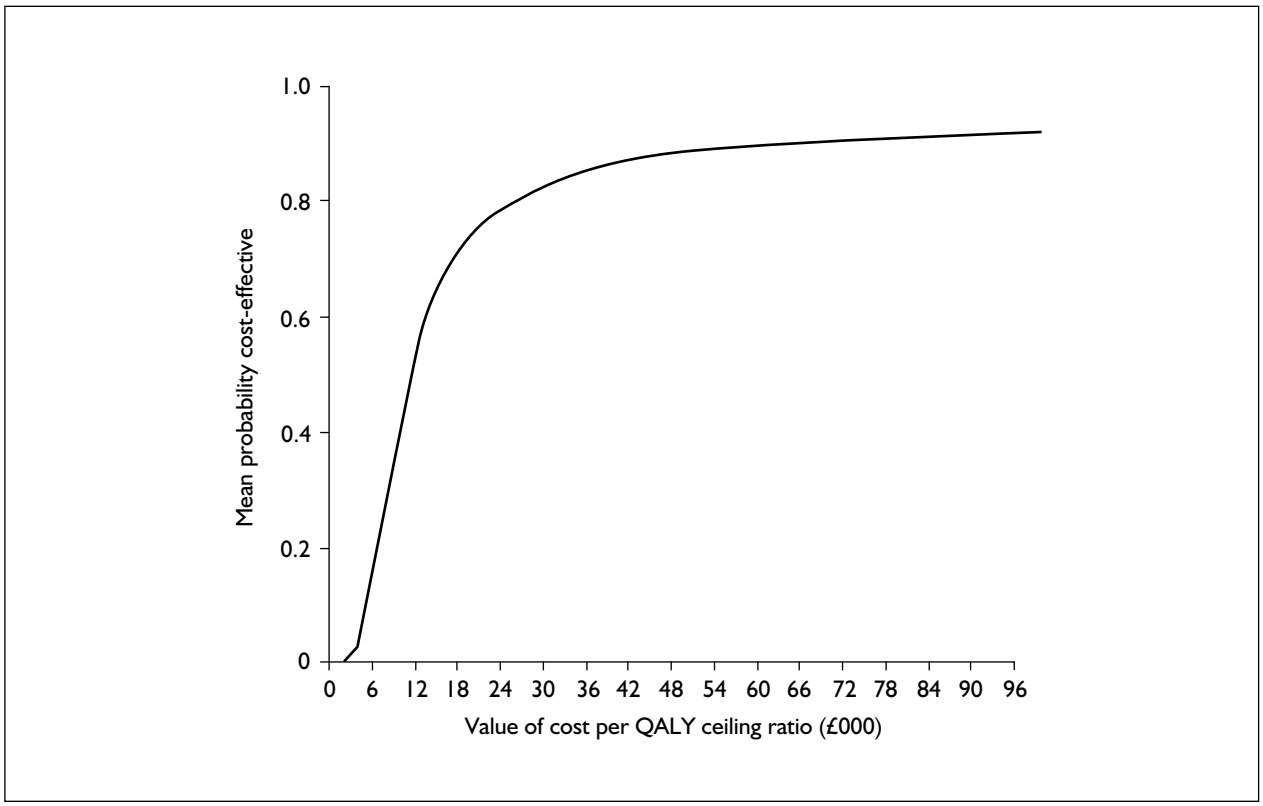


FIGURE 24 *CEAC for LTG relative to CBZ*

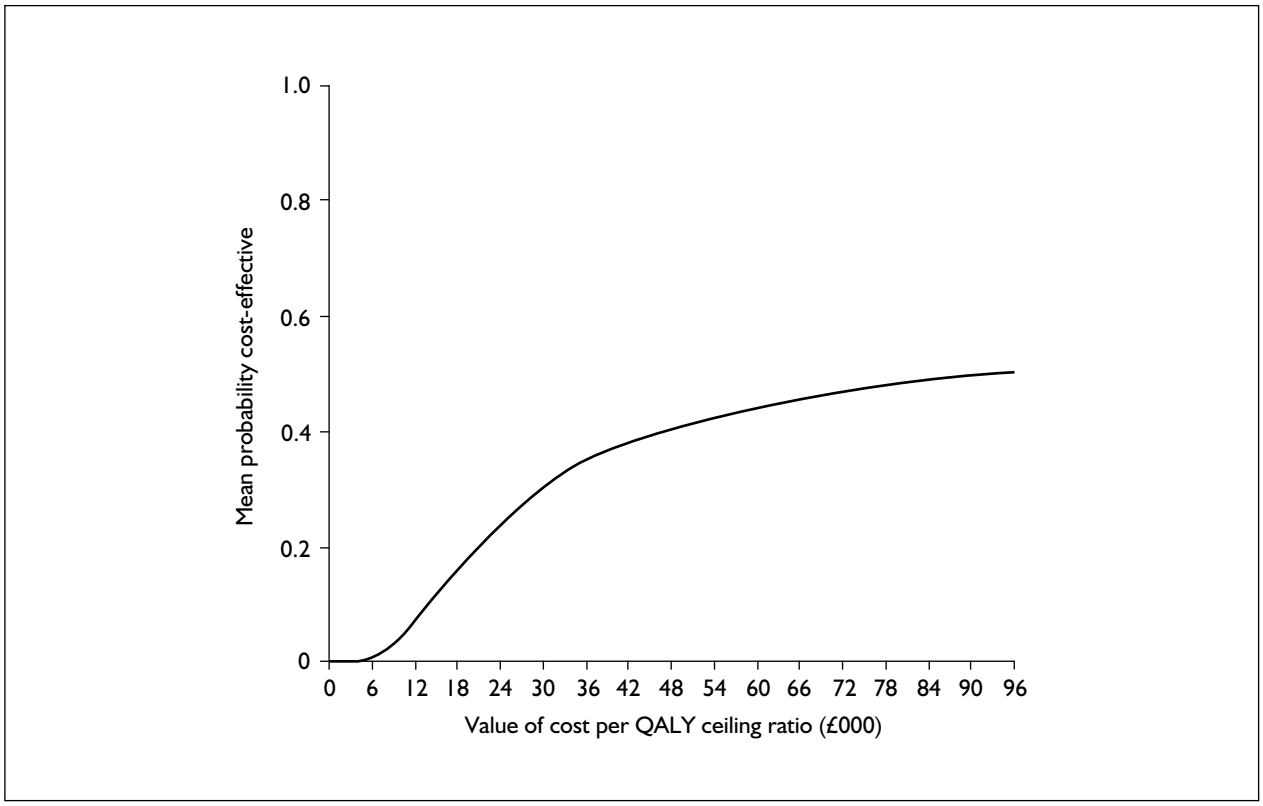


FIGURE 25 *CEAC for GBP relative to CBZ*

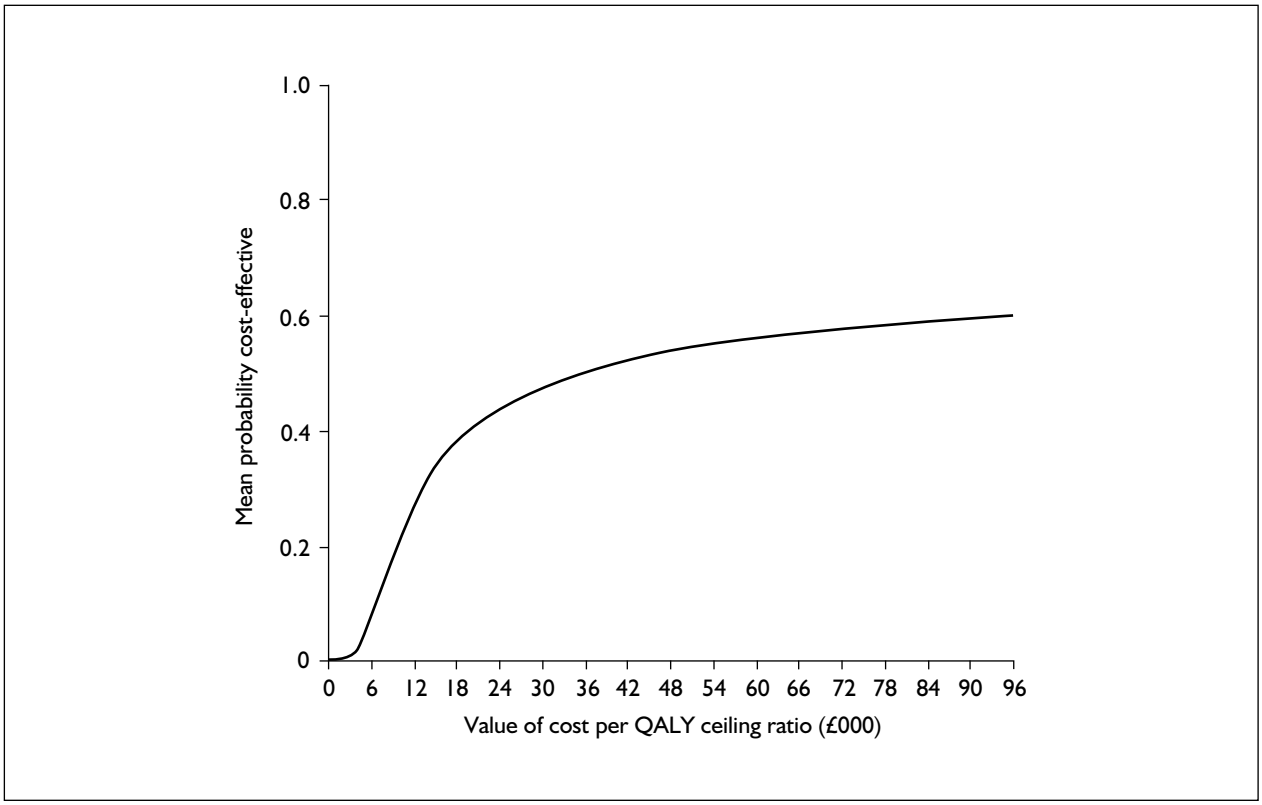


FIGURE 26 *CEAC for TPM relative to CBZ*

TABLE 34 *Probabilities that the new AEDs are cost-effective relative to CBZ across a range of ceiling ratios (λ)*

Ceiling ratio, λ (£)	Probability new AED is cost-effective		
	GBP	LTG	TPM
10,000	0.04	0.42	0.20
30,000	0.31	0.82	0.47
50,000	0.41	0.89	0.54

= 91, GBP = 107, LTG = 70, OXC = 72, and TPM = 74.

Table 35 shows the breakdown of hospitalisation resource use and 'other' resource use among patients when OXC is included.

Table 36 shows the contribution of AED costs, hospitalisation costs and 'other' costs to the average cost per patient.

Table 37 shows the point estimates of the ICERs for the new AEDs when OXC is included in the comparison. As previously, these ICERs are estimated using the lowest costs for CBZ and LTG (CBZ_{low} and LTG_{low}).

Both TPM and GBP have positive incremental costs and negative incremental QALY gains and are therefore dominated by OXC and LTG, respectively; LTG is ruled out on the grounds of extended dominance. The ICER for OXC relative to CBZ is £6200.

The same pattern of results is found when using different combinations of high and low costs for CBZ and LTG. The lowest value of the ICER for OXC is when CBZ_{high} and LTG_{low} are used and is equal to £5,702. The highest value for the ICER for OXC is when CBZ_{low} and LTG_{high} are used and is equal to £6351.

The results of the sensitivity analysis on the assumptions made in the AUC approach to estimating QALYs did not impact on the relative ICERs (and therefore the pattern of results). The baseline estimate of the ICER for OXC relative to CBZ (£6200) ranged from £5952 to £6526 depending on the assumptions made.

Cost-effectiveness acceptability curves. Bootstrapping the baseline point estimate of the ICER for OXC relative to CBZ results in 92% of the replications being located in the NE quadrant of the cost-effectiveness plane (more costly, more effective), with the remaining 8% being

ABLE 35 *Breakdown of resource use (O C included)*

Item of resource use	Number of patients reporting contact	verage number of contacts among patients reporting contact (95% CI)			
Hospitalisations					
sychiatric ward					
Medical ward	1.5 (–4.9 to 7.9)			7.3 (–2.7 to 17.4)	20.7 (–12.2 to 53.6)
Surgical ward			7 (–43.8 to 57.8)		9.5 (–85.8 to 104.8)
		1.3 (–0.1 to 2.8)			1.3 (–0.1 to 2.8)
Other		11 (–27.1 to 49.1)			
Other					
Nurse at GP surgery	6.5 (4.7 to 8.4)	6.1 (3.1 to 9.1)	7.8 (4.0 to 11.7)	6.4 (4.2 to 8.6)	6.8 (4.4 to 9.2)
GP at surgery	9.5 (6.6 to 12.4)	8.2 (5.9 to 10.4)	8.9 (5.4 to 12.4)	8.3 (5.3 to 11.3)	6.9 (5.4 to 8.4)
Nurse at home	2.4 (1.5 to 3.3)	4.2 (1.2 to 7.2)	4.3 (1.1 to 7.6)	3.9 (2.1 to 5.7)	6.5 (4.0 to 8.9)
GP at home	2.8 (–0.7 to 6.2)	3.0 (–0.9 to 6.9)	4.2 (3.2 to 5.2)	3.0 (1.9 to 4.1)	3.3 (2.1 to 4.5)
Ambulance	4.4 (1.9 to 6.8)	5.0 (0.9 to 9.1)	3.7 (2.3 to 5.1)	4.2 (2.5 to 5.9)	4.1 (3.0 to 5.3)
Blood test	4.2 (3.2 to 5.2)	6.5 (4.5 to 8.5)	4.9 (2.7 to 7.2)	7.6 (3.7 to 11.6)	4.3 (3.2 to 5.4)
Urine test	3.8 (1.9 to 5.6)	3.5 (1.8 to 5.2)	3.4 (2.7 to 4.1)	4.7 (2.6 to 6.9)	4.3 (2.5 to 6.1)
Ultrasound		2.5 (–0.9 to 4.9)	2.3 (–.03 to 4.9)	2.0 (0.9 to 3.1)	3.0 (1.0 to 5.0)
-ray	2.6 (1.3 to 4.0)	2.6 (1.2 to 4.0)	1.5 (0.8 to 2.2)	4.2 (2.2 to 6.2)	5.3 (3.3 to 7.4)
CT scan	1.8 (1.2 to 2.5)	2.1 (1.5 to 2.7)	2.2 (1.1 to 3.3)	2.2 (1.3 to 3.1)	2.3 (1.4 to 3.1)
MRI scan	1.7 (1.2 to 2.3)	2.1 (1.5 to 2.6)	2.5 (1.7 to 3.3)	2.7 (1.8 to 3.6)	2.6 (1.8 to 3.4)
	1.4 (1.0 to 1.8)	1.4 (1.1 to 1.8)	1.6 (1.1 to 2.1)	2.0 (1.2 to 2.8)	2.3 (1.6 to 3.0)
Health visitor	2.0 (0.1 to 4.0)			6.0 (0.1 to 11.9)	
Social worker	5.5 (0.6 to 10.4)		6.3 (3.1 to 9.6)	4.7 (3.4 to 6.0)	3.0 (1.4 to 4.6)
Disablement resettlement officer	4.0 (0.1 to 7.9)				
sychologist	4.3 (2.3 to 6.4)		10.0 (0.9 to 19.1)	3.9 (0.7 to 7.1)	3.0 (1.6 to 4.3)
Counsellor	10.7 (–6.4 to 27.7)	4.0 (1.7 to 6.3)	14.2 (–1.4 to 29.8)	7.3 (3.6 to 10.9)	8.6 (3.5 to 13.7)
Educational/vocational officer					

[a] esource use associated with the management of adverse events requiring hospitalisation.
[b] Other healthcare and social services resource use.

TABLE 36 *The contribution of AED costs, hospitalisation costs and 'other' costs to the average cost per patient*

AED	Average cost per patient (£) (95% CI)	Breakdown of average cost per patient (£) (95% CI)		
		AEDs	Hospitalisation[a]	Other[b]
CBZ	1095 (860 to 1330)	444 (323 to 565)	59 (–48 to 167)	592 (441 to 743)
OXC	1839 (1481 to 2197)	978 (883 to 1073)	294 (38 to 550)	567 (406 to 728)
TPM	1930 (1536 to 2324)	1064 (910 to 1218)	144 (–32 to 321)	722 (477 to 966)
LTG	2078 (1740 to 2416)	1212 (1073 to 1350)	102 (–14 to 219)	764 (499 to 1029)
GBP	2573 (1929 to 3216)	1439 (1279 to 1599)	415 (–166 to 996)	719 (538 to 900)

[a] Costs associated with the management of adverse events requiring hospitalisation.
[b] Other healthcare and social services costs.

TABLE 37 *ICERs for the new AEDs (OXC included)*

AED	Cost (£) (95% CI)	QALYs (95% CI)	Incremental cost (£)	Incremental QALYs	ICER (£/QALY)
CBZ	1095 (860 to 1330)	1.491 (1.38 to 1.60)	–	–	–
OXC	1839 (1481 to 2197)	1.611 (1.50 to 1.72)	744	0.12	6200
TPM	1930 (1536 to 2324)	1.541 (1.42 to 1.66)	91	–0.07	Dominated
LTG	2078 (1740 to 2416)	1.563 (1.45 to 1.67)	148	0.022	6727 extended dominance
GBP	2573 (1929 to 3216)	1.480 (1.37 to 1.59)	495	–0.083	Dominated

TABLE 38 *Probabilities that the new AEDs are cost-effective relative to CBZ across a range of ceiling ratios (λ)*

Ceiling ratio, λ (£)	Probability new AED is cost-effective			
	GBP	LTG	OXC	TPM
10,000	0.04	0.36	0.69	0.39
30,000	0.21	0.66	0.86	0.63
50,000	0.30	0.73	0.89	0.67

located in the NW quadrant (more costly, less effective).

Figure 27 shows the CEAC for OXC relative to CBZ. As above, in order to provide a comparative context for the CEAC for OXC, *Figures 28–30* show the respective CEACs for GBP, LTG and TPM relative to CBZ. The probabilities that each of the new AEDs is cost-effective at ceiling ratios of £10,000, £30,000 and £50,000 per QALY are presented in *Table 38*.

Cost per seizure avoided analysis, adults and children combined

CBZ, GBP, LTG, TPM

This analysis is based on 823 patients, with the numbers of patients in each drug group being: CBZ = 210, GBP = 217, LTG = 200, and TPM = 196.

Table 39 shows the breakdown of hospitalisation resource use and 'other' resource use among patients when OXC is excluded.

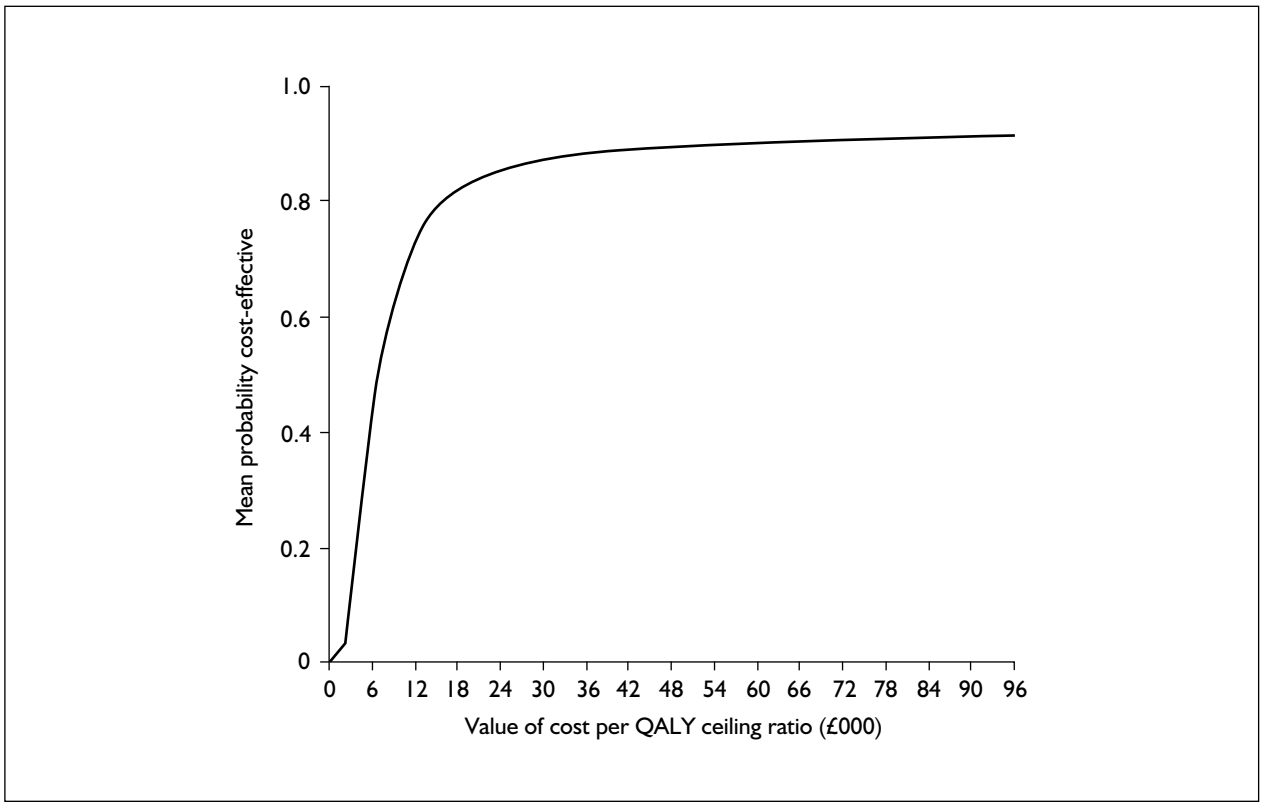


FIGURE 27 *CEAC for OXC relative to CBZ*

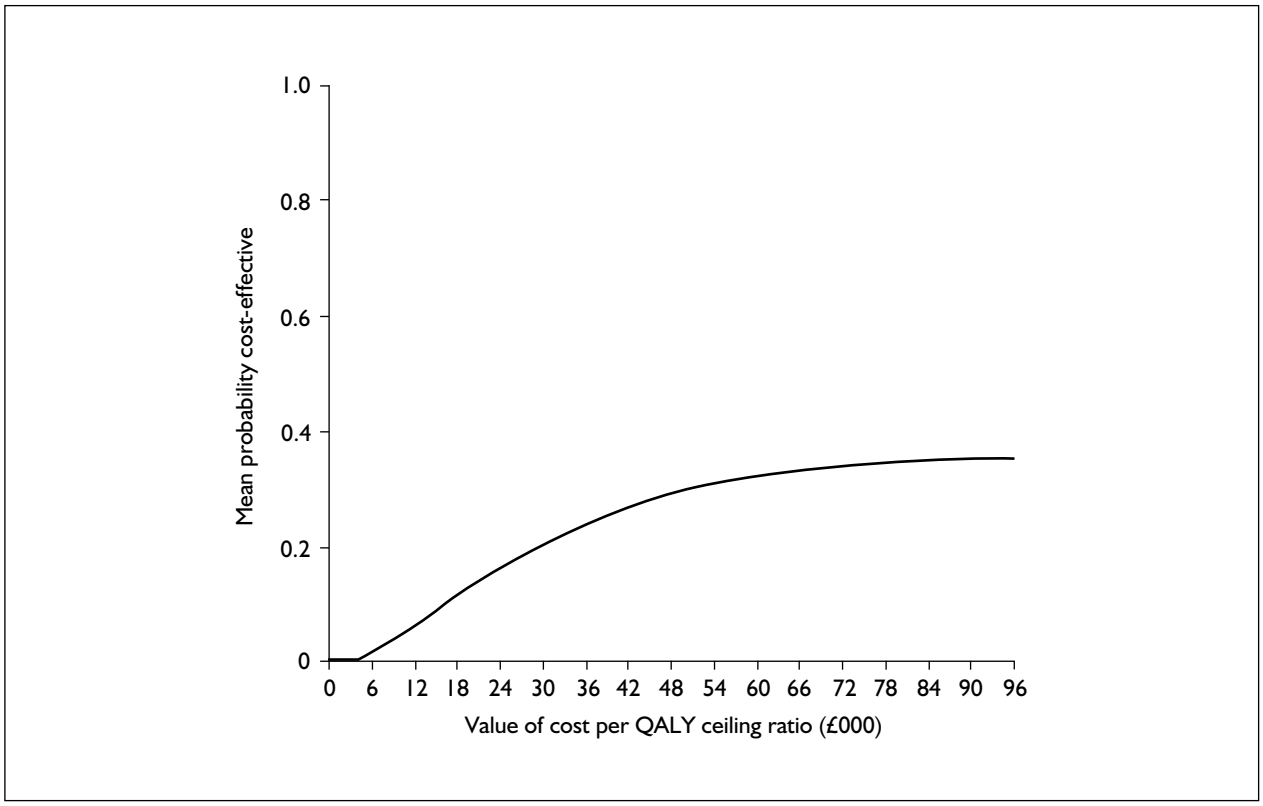


FIGURE 28 *CEAC for GBP relative to CBZ*

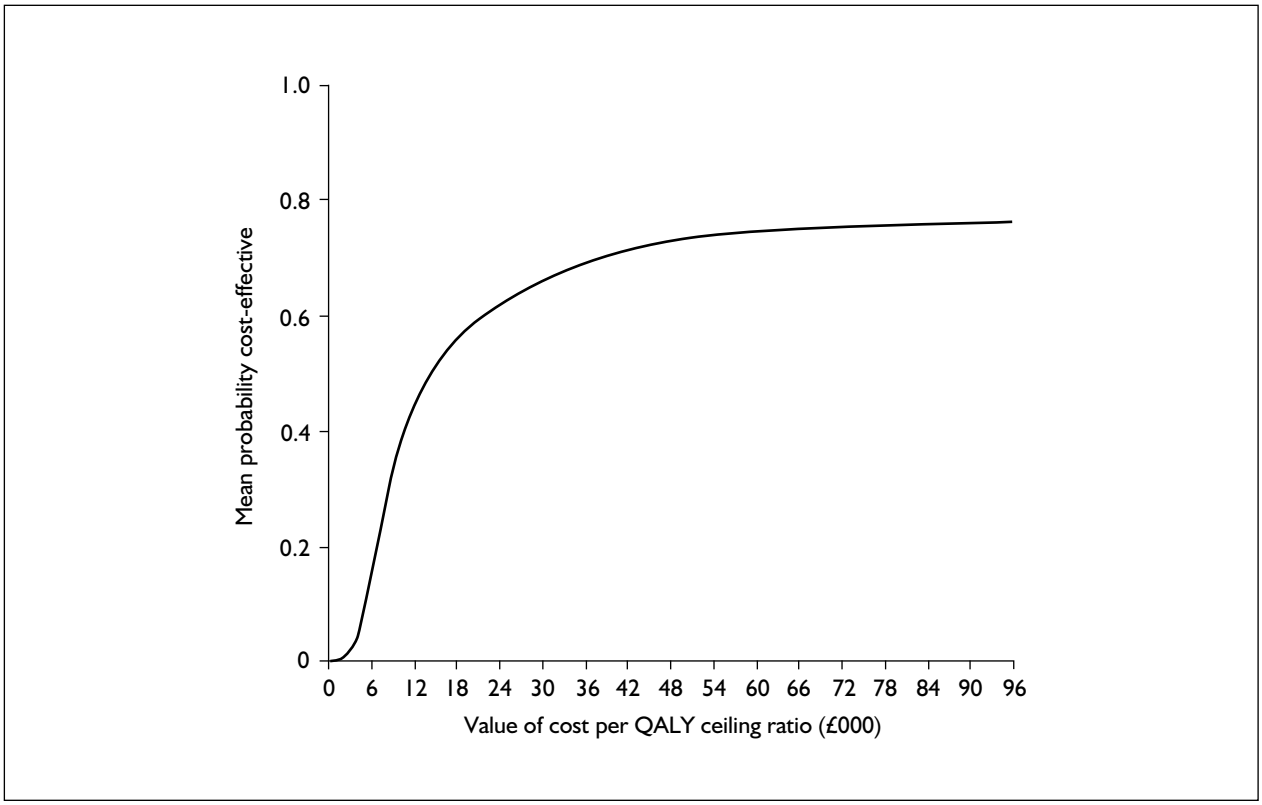


FIGURE 29 *CEAC for LTG relative to CBZ*

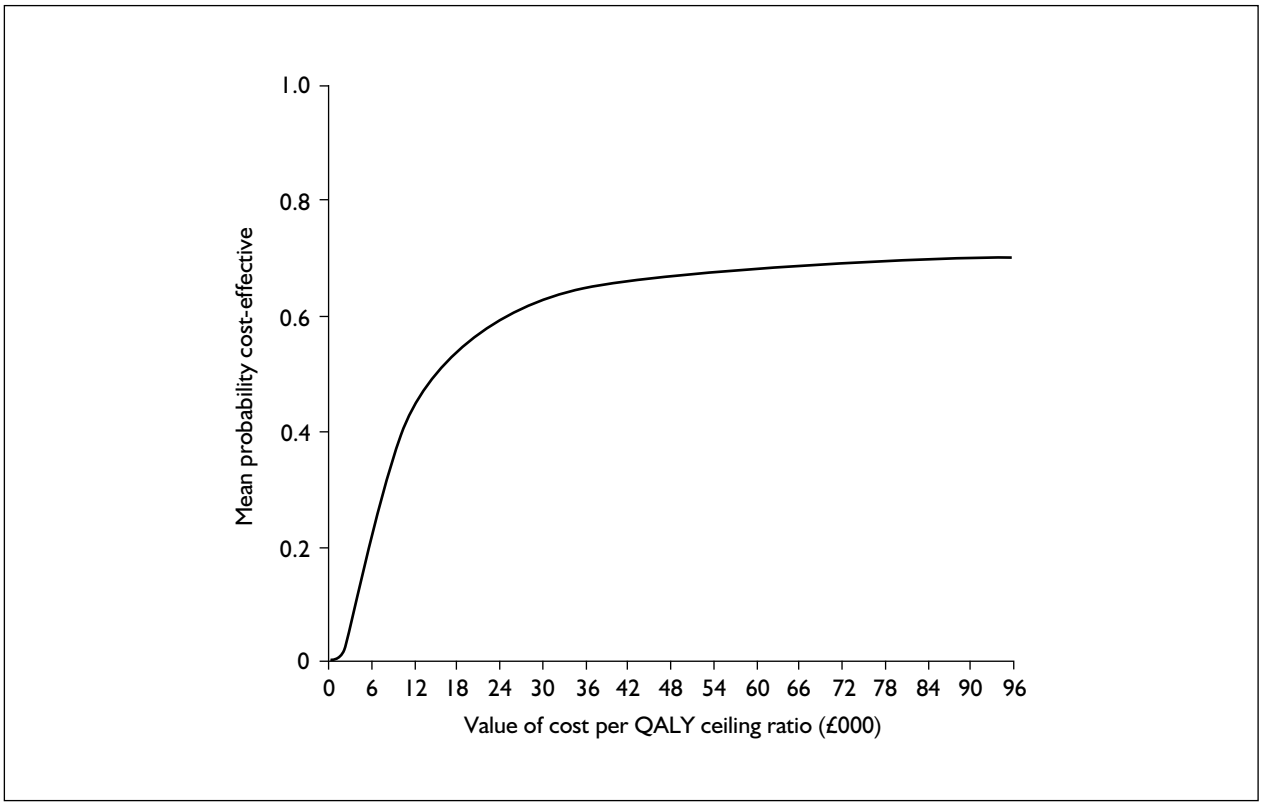


FIGURE 30 *CEAC for TPM relative to CBZ*

ABLE 39 *Breakdown of resource use (O C excluded)*

Item of resource use	Number of patients reporting contact	verage number of contacts among patients reporting contact (95% CI)			
Hospitalisations					
ICU					
sychiatric ward					
Medical ward		8.5 (–0.4 to 17.4)	6.2 (–3.1 to 15.4)	9.1 (3.9 to 14.4)	14.1 (–5.4 to 33.6)
Surgical ward		5.5 (–3.2 to 14.2)	9.3 (–0.6 to 19.1)	2.8 (0.4 to 5.1)	5.6 (0.8 to 10.4)
					1.1 (0.8 to 1.5)
Other		2 (–2.3 to 6.3)	6.5 (–38.0 to 51.0)	5.2 (–1.24 to 11.6)	2 (–0.2 to 4.2)
Other					
Nurse at GP surgery		7.1 (5.2 to 9.0)	9.1 (5.0 to 13.2)	11.4 (1.0 to 21.7)	5.9 (4.3 to 7.4)
GP at surgery		9.7 (7.7 to 11.6)	8.2 (6.4 to 10.1)	10.5 (5.6 to 15.4)	7.5 (6.4 to 8.6)
Nurse at home		2.6 (1.8 to 3.3)	3.9 (1.8 to 6.1)	3.3 (2.1 to 4.5)	7.2 (4.0 to 10.4)
GP at home		3.6 (1.9 to 5.4)	4.1 (2.7 to 5.6)	2.9 (2.1 to 3.8)	3.4 (2.6 to 4.1)
Ambulance		5.2 (3.2 to 7.2)	4.9 (3.1 to 6.7)	4.5 (1.6 to 7.4)	5.2 (3.4 to 6.9)
Blood test		5.2 (3.8 to 6.6)	5.0 (3.7 to 6.4)	5.4 (3.8 to 7.0)	4.2 (3.6 to 4.8)
Urine test		4.9 (2.7 to 7.0)	3.2 (2.6 to 3.9)	3.4 (2.0 to 4.7)	3.5 (2.5 to 4.3)
Ultrasound		1.8 (0.8 to 2.9)	1.8 (0.9 to 2.7)	3.0 (1.0 to 5.0)	2.0 (0.8 to 3.2)
-ray		3.8 (1.9 to 5.6)	2.6 (1.7 to 3.6)	3.3 (2.2 to 4.5)	5.4 (3.6 to 7.2)
CT scan		1.9 (1.4 to 2.3)	2.7 (1.8 to 3.5)	1.9 (1.4 to 2.5)	2.3 (1.7 to 2.9)
MRI scan		2.0 (1.6 to 2.4)	2.7 (2.0 to 3.4)	2.3 (1.8 to 2.7)	2.8 (2.2 to 3.4)
		1.4 (1.1 to 1.8)	1.9 (1.4 to 2.3)	1.7 (1.2 to 2.2)	2.2 (1.7 to 2.6)
Health visitor		4.4 (–0.7 to 9.6)		9.2 (–0.3 to 18.7)	
Social worker		4.4 (3.2 to 5.6)	4.6 (2.1 to 7.0)	5.6 (4.1 to 7.1)	3.0 (1.7 to 4.3)
Disablement					
resettlement officer		3.5 (1.6 to 5.4)			3.5 (0.3 to 6.8)
sychologist		4.1 (2.6 to 5.6)	5.6 (1.6 to 9.6)	4.6 (2.0 to 7.3)	6.4 (2.6 to 10.2)
Counsellor		10.0 (3.9 to 16.1)	7.8 (0.2 to 15.4)	4.8 (2.2 to 7.3)	10.8 (1.6 to 20.0)
Educational/vocational officer		9.0 (7.1 to 11.0)	8.3 (1.7 to 15.0)	2.8 (1.0 to 4.6)	11.8 (–2.3 to 25.8)

[a] esource use associated with the management of adverse events requiring hospitalisation.
[b] Other healthcare and social services resource use.

TABLE 40 *The contribution of AED costs, hospitalisation costs and 'other' costs to the average cost per patient*

AED	Average cost per patient (£) (95% CI)	Breakdown of average cost per patient (£) (95% CI)		
		AEDs	Hospitalisation[a]	Other[b]
CBZ	1266 (1030 to 1502)	405 (330 to 481)	185 (15 to 355)	676 (551 to 801)
TPM	2008 (1693 to 2322)	1508 (961 to 1155)	226 (–5 to 456)	724 (571 to 877)
LTG	2134 (1890 to 2378)	1212 (1127 to 1297)	195 (50 to 339)	727 (548 to 907)
GBP	2494 (2144 to 2844)	1460 (1353 to 1568)	250 (–40 to 540)	784 (641 to 926)

[a] Costs associated with the management of adverse events requiring hospitalisation.
[b] Other healthcare and social services costs.

TABLE 41 *ICERs for the new AEDs (OXC excluded)*

AED	Cost (£)	Seizures	Incremental cost (£)	Incremental seizures avoided	ICER (£/seizure avoided)
CBZ	1266 (1030 to 1502)	52.6 (36.0 to 69.2)	–	–	–
TPM	2008 (1693 to 2322)	63.1 (32.9 to 93,3)	742	–10.5	Dominated
LTG	2134 (1890 to 2378)	41.7 (28.0 to 55.4)	126	21.4	80
GBP	2494 (2144 to 2844)	69.8 (38.9 to 100.7)	360	–28.1	Dominated

Table 40 shows the contribution of AED costs, hospitalisation costs and 'other' costs to the average cost per patient.

Table 41 shows the point estimates of the ICERs for the new AEDs. As with the cost per QALY analysis, these ICERs are estimated using the lowest costs for CBZ and LTG (CBZ_{low} and LTG_{low}).

TPM and GBP have positive incremental costs and a negative incremental number of seizures avoided and are therefore dominated by CBZ and LTG, respectively. The ICER for LTG relative to CBZ is £80.

The same pattern of results is found when using different combinations of high and low costs for CBZ and LTG. The lowest value of the ICER for LTG is when CBZ_{high} and LTG_{low} are used and is equal to £74. The highest value of the ICER for LTG is when CBZ_{low} and LTG_{high} are used and is equal to £96.

Cost-effectiveness acceptability curves. Bootstrapping the point estimate of the ICER for LTG relative to CBZ results in 85% of the replications being located in the NE quadrant of the cost-effectiveness plane (more costly, more effective), with the remaining 15% being located in the NW quadrant (more costly, less effective).

The CEAC for LTG relative to CBZ is shown in *Figure 31*. By way of providing a comparative context for this CEAC, *Figures 32* and *33* show the respective CEACs for GBP and TPM relative to CBZ. The probabilities that each of the new AEDs is cost-effective at ceiling ratios of £160, £400, £800 and £1600 per seizure avoided are presented in *Table 42*.

CBZ, GBP, LTG, OXC, TPM

This analysis is based on 547 patients, with the numbers of patients in each drug group being CBZ = 112, GBP = 130, LTG = 100, OXC = 103 and TPM = 102.

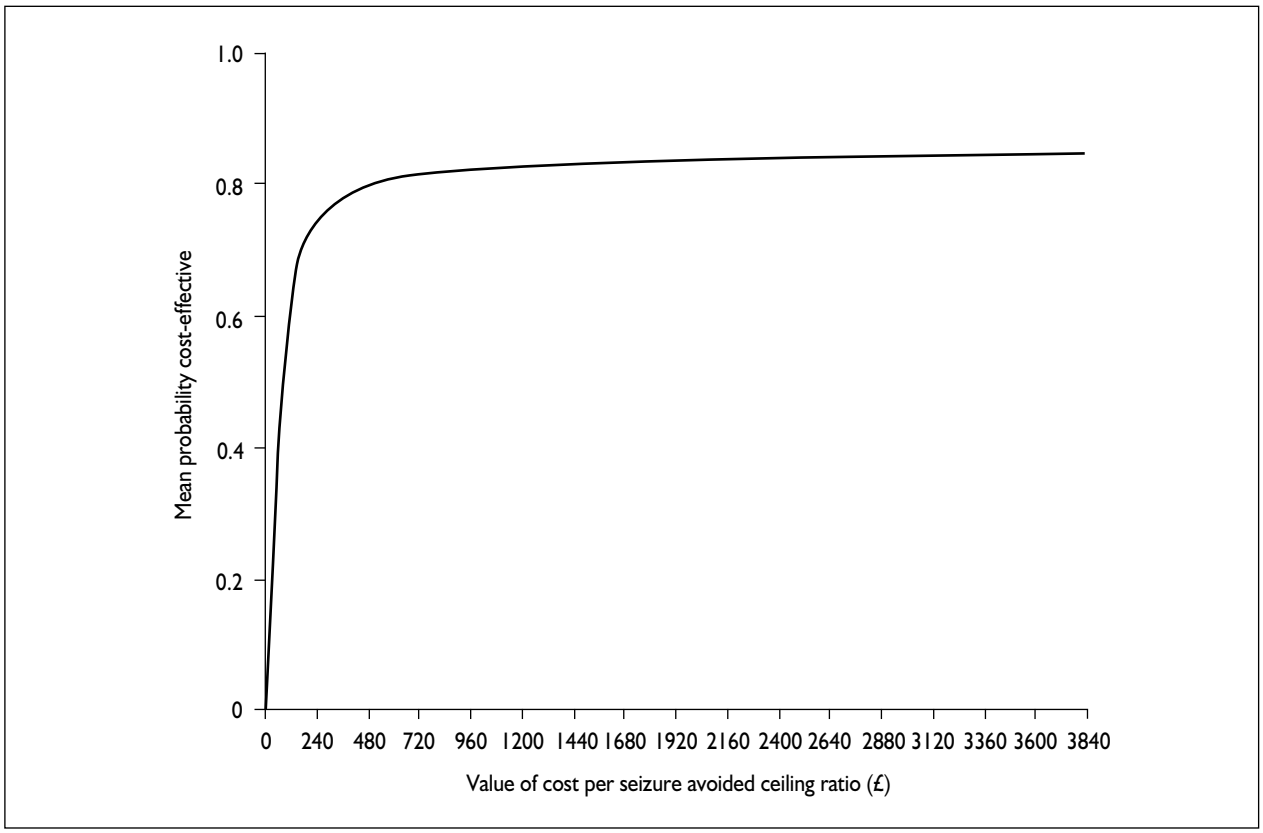


FIGURE 31 *CEAC for LTG relative to CBZ*

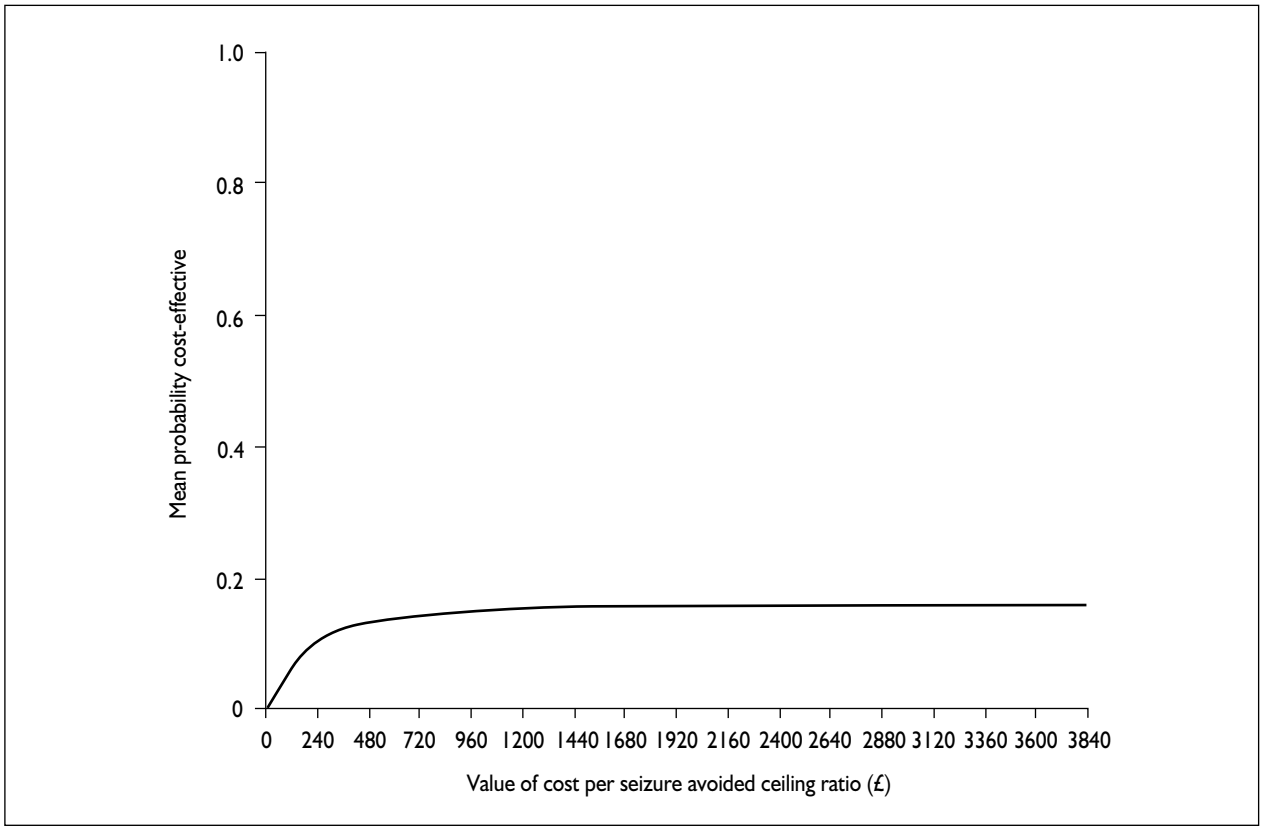


FIGURE 32 *CEAC for GBP relative to CBZ*

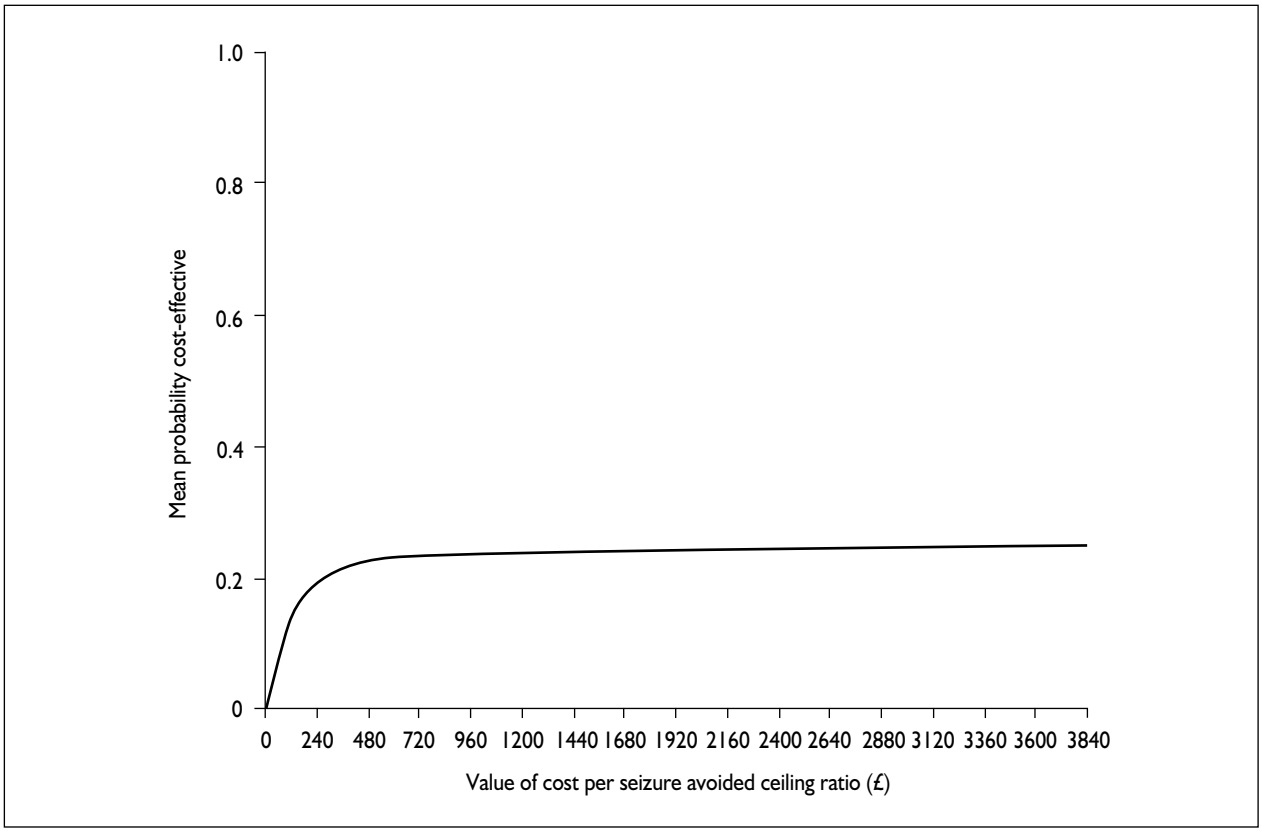


FIGURE 33 *CEAC for TPM relative to CBZ*

TABLE 42 *Probabilities that the new AEDs are cost-effective across a range of ceiling ratios (λ)*

Ceiling ratio, λ (£)	Probability new AED is cost-effective		
	GBP	LTG	TPM
160	0.08	0.70	0.17
400	0.13	0.79	0.22
800	0.15	0.82	0.24
1600	0.16	0.84	0.25

Table 43 shows the breakdown of hospitalisation resource use and 'other' resource use among patients when OXC is included.

Table 44 shows the contribution of AED costs, hospitalisation costs and 'other' costs to the average cost per patient.

Table 45 shows the point estimates of the ICERs for the new AEDs when OXC is included in the comparison. As previously, these ICERs are estimated using the lowest costs for CBZ and LTG (CBZ_{low} and LTG_{low}).

LTG, TPM and GBP have positive incremental costs and negative incremental seizures avoided and are therefore dominated by OXC. The ICER for OXC relative to CBZ is £35.

The same pattern of results is found when using different combinations of high and low costs for CBZ and LTG. The lowest value of the ICER for OXC is when CBZ_{high} and LTG_{low} are used and is equal to £31. The highest value for the ICER for OXC is when CBZ_{high} and LTG_{low} are used and is equal to £36.

Cost-effectiveness acceptability curves. Bootstrapping the point estimate of the ICER for OXC relative to CBZ results in 91% of the replications being located in the NE quadrant of the cost-effectiveness plane (more costly, more effective), with the remaining 9% being located in the NW quadrant (more costly, less effective).

Figure 34 shows the CEAC for OXC relative to CBZ. As above, in order to provide a comparative context for the CEAC for OXC, *Figures 35–37* show the respective CEACs for GBP, LTG and TPM relative to CBZ. The probabilities that each of the new AEDs is cost-effective at ceiling ratios of £160, £400, £800 and £1600 per seizure avoided are presented in *Table 46*.

ABLE 43 *Breakdown of resource use (O C included)*

Item of resource use	Number of patients reporting contact	verage number of contacts among patients reporting contact (95% CI)			
Hospitalisations					
ICU					
sychiatric ward					
Medical ward	11 (–29.9 to 51.9)	4.6 (1.5 to 7.7)	9.7 (–21.2 to 40.5)	7.3 (–2.7 to 17.4)	23.5 (–16.5 to 63.5)
Surgical ward		7 (–11.0 to 25.0)	11 (–9.3 to 31.3)		
		1.3 (0.5 to 2.0)			1.2 (0.6 to 1.8)
Other		8 (–6.9 to 22.9)	6.5 (–38.0 to 51.0)	6.5 (–63.4 to 76.4)	
Other					
Nurse at GP surgery	6.1 (4.3 to 7.9)	6.3 (3.6 to 8.9)	7.1 (3.9 to 10.2)	5.9 (4.0 to 7.7)	6.4 (4.3 to 8.4)
GP at surgery	9.3 (6.7 to 11.8)	8.6 (6.5 to 10.7)	8.2 (5.4 to 11.1)	7.6 (5.1 to 10.1)	7.8 (6.2 to 9.5)
Nurse at home	2.7 (1.8 to 3.5)	3.8 (1.3 to 6.4)	4.3 (1.4 to 7.2)	3.5 (2.0 to 5.0)	6.3 (4.0 to 8.6)
GP at home	2.8 (–0.7 to 6.2)	3.3 (1.0 to 5.7)	3.7 (2.4 to 5.0)	3.0 (1.9 to 4.1)	3.3 (2.2 to 4.3)
Ambulance	4.3 (2.0 to 6.6)	5.0 (1.9 to 8.1)	3.9 (2.6 to 5.3)	3.8 (2.4 to 5.1)	5.6 (3.1 to 8.1)
Blood test	4.3 (3.4 to 5.2)	6.5 (4.8 to 8.3)	5.1 (3.1 to 7.0)	6.7 (3.4 to 9.9)	4.4 (3.5 to 5.4)
Urine test	3.5 (1.9 to 5.1)	3.5 (1.8 to 5.2)	3.3 (2.5 to 4.0)	4.2 (2.3 to 6.2)	4.0 (2.4 to 5.6)
Ultrasound	1.5 (0.5 to 2.5)	2.3 (0.8 to 3.7)	2.5 (0.6 to 4.4)	1.7 (0.9 to 2.5)	3.0 (1.0 to 5.0)
-ray	2.7 (1.5 to 3.9)	2.6 (1.2 to 4.0)	1.5 (0.8 to 2.2)	3.7 (2.2 to 5.2)	5.0 (3.0 to 7.0)
CT scan	1.8 (1.3 to 2.4)	2.2 (1.6 to 2.8)	2.1 (1.2 to 3.1)	2.0 (1.3 to 2.8)	2.4 (1.6 to 3.1)
MRI scan	1.8 (1.3 to 2.3)	2.1 (1.5 to 2.6)	2.4 (1.6 to 3.1)	2.6 (1.8 to 3.4)	2.7 (2.0 to 3.4)
	1.5 (1.1 to 1.9)	1.9 (1.3 to 2.4)	1.6 (1.1 to 2.0)	1.8 (1.2 to 2.5)	2.4 (1.7 to 3.0)
Health visitor	2.0 (0.1 to 4.0)			10.5 (–1.3 to 22.3)	
Social worker	5.0 (2.0 to 8.0)		5.0 (1.5 to 8.5)	4.7 (3.4 to 6.0)	3.0 (1.7 to 4.3)
Disablement resettlement officer	4.0 (0.1 to 7.9)				
sychologist	3.9 (1.9 to 5.8)	3.0 (0.7 to 5.3)	6.8 (0.5 to 13.0)	4.0 (1.2 to 6.9)	3.0 (1.7 to 4.3)
Counsellor	11.0 (–1.1 to 23.1)	4.0 (1.7 to 6.3)	12.3 (–0.9 to 25.5)	7.3 (3.6 to 10.9)	7.4 (3.5 to 11.3)
Educational/vocational officer					

[a] esource use associated with the management of adverse events requiring hospitalisation.
[b] Other healthcare and social services resource use.

TABLE 44 *The contribution of AED costs, hospitalisation costs and 'other' costs to the average cost per patient*

AED	Average cost per patient (£) (95% CI)	Breakdown of average cost per patient (£) (95% CI)		
		AEDs	Hospitalisation[a]	Other[b]
CBZ	1151 (880 to 1423)	419 (315 to 524)	131 (–52 to 314)	601 (468 to 734)
OXC	1815 (1541 to 2089)	966 (878 to 1054)	234 (51 to 416)	615 (482 to 749)
LTG	1946 (1683 to 2209)	1134 (1018 to 1250)	111 (2 to 220)	701 (501 to 900)
TPM	2059 (1578 to 2539)	1003 (876 to 1130)	295 (–97 to 686)	761 (558 to 963)
GBP	2594 (2048 to 3139)	1456 (1313 to 1597)	343 (–136 to 821)	795 (601 to 989)

[a] Costs associated with the management of adverse events requiring hospitalisation.
[b] Other healthcare and social services costs.

TABLE 45 *ICERs for the new AEDs (OXC included)*

AED	Cost (£) (95% CI)	Seizures (95% CI)	Incremental cost (£)	Incremental seizures avoided	ICER (£/seizure avoided)
CBZ	1151 (880 to 1423)	50.9 (26.7 to 75.2)	–	–	–
OXC	1815 (1541 to 2089)	32.0 (17.8 to 46.3)	664	18.9	35
LTG	1946 (1683 to 2209)	50.9 (27.3 to 74.5)	131	–18.9	Dominated
TPM	2059 (1578 to 2539)	59.4 (25.3 to 93.5)	113	–8.5	Dominated
GBP	2594 (2048 to 3139)	85.3 (35.1 to 135.4)	535	–25.9	Dominated

TABLE 46 *Probabilities that the new AEDs are cost-effective relative to CBZ across a range of ceiling ratios (λ)*

Ceiling ratio, λ (£)	Probability new AED is cost-effective			
	GBP	LTG	OXC	TPM
160	0.05	0.41	0.85	0.27
400	0.08	0.48	0.90	0.33
800	0.10	0.50	0.90	0.35
1600	0.10	0.52	0.91	0.37

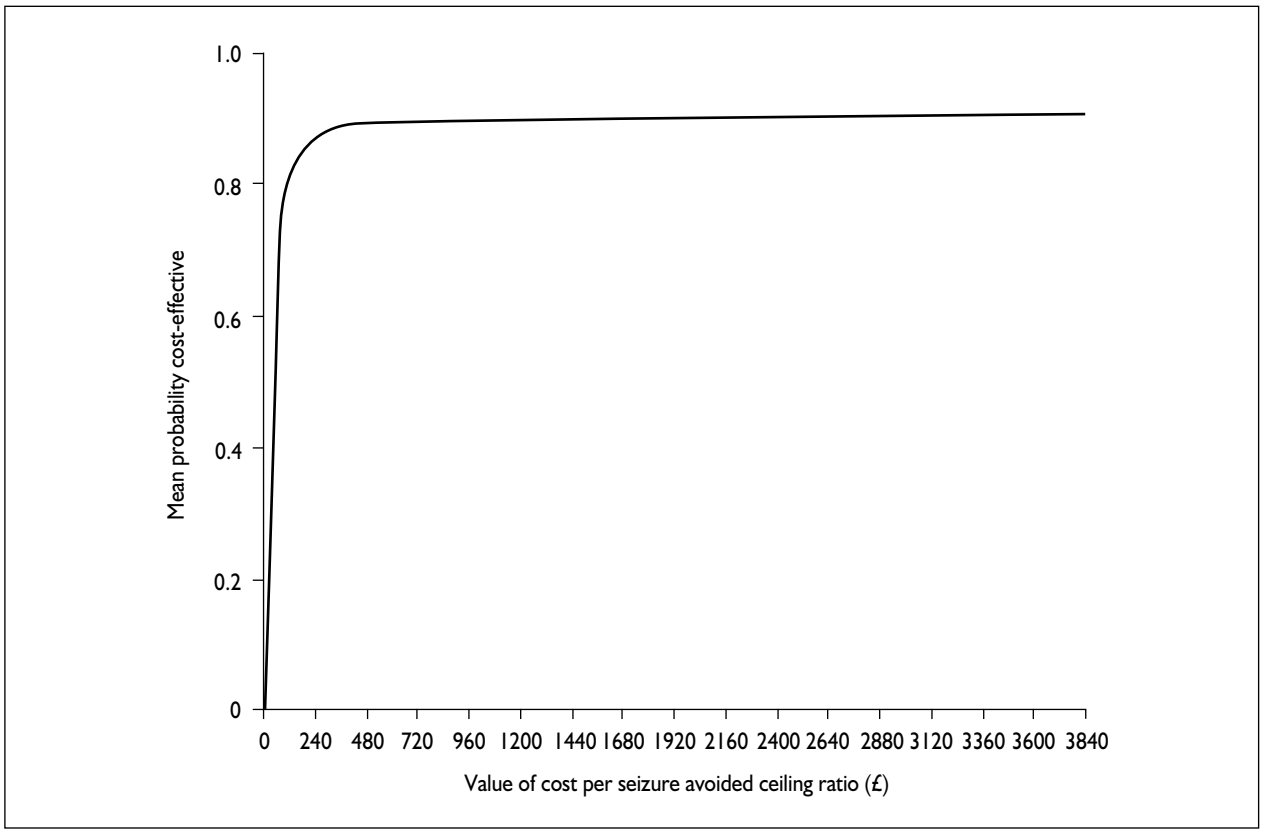


FIGURE 34 *CEAC for OXC relative to CBZ*

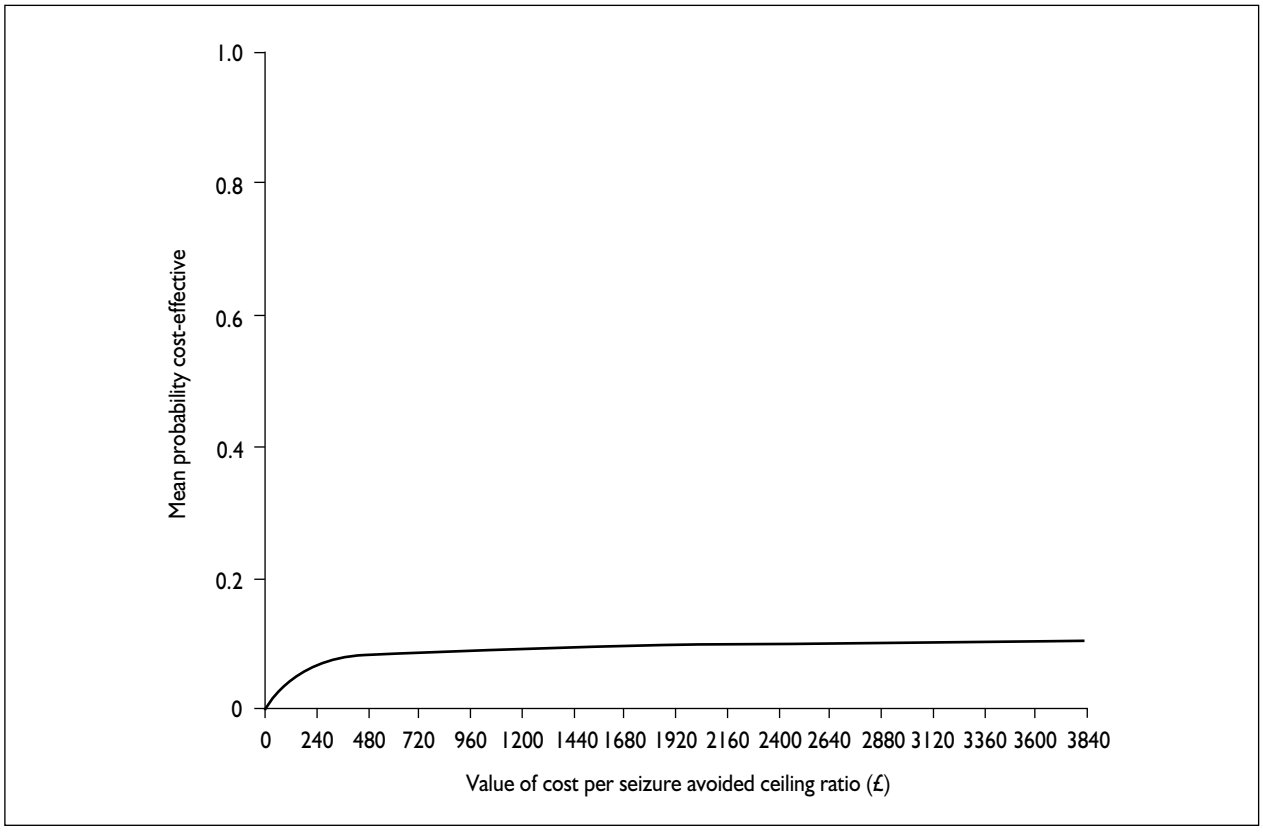


FIGURE 35 *CEAC for GBP relative to CBZ*

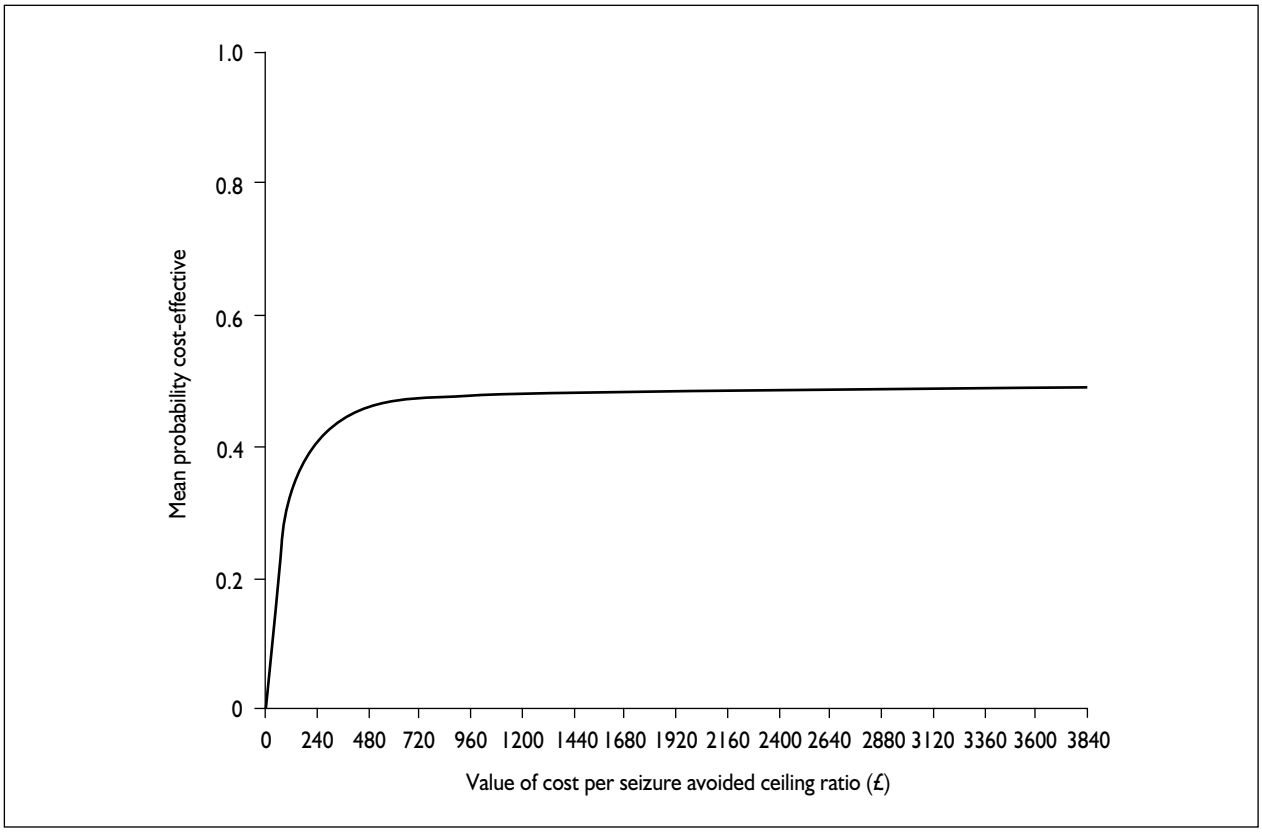


FIGURE 36 *CEAC for LTG relative to CBZ*

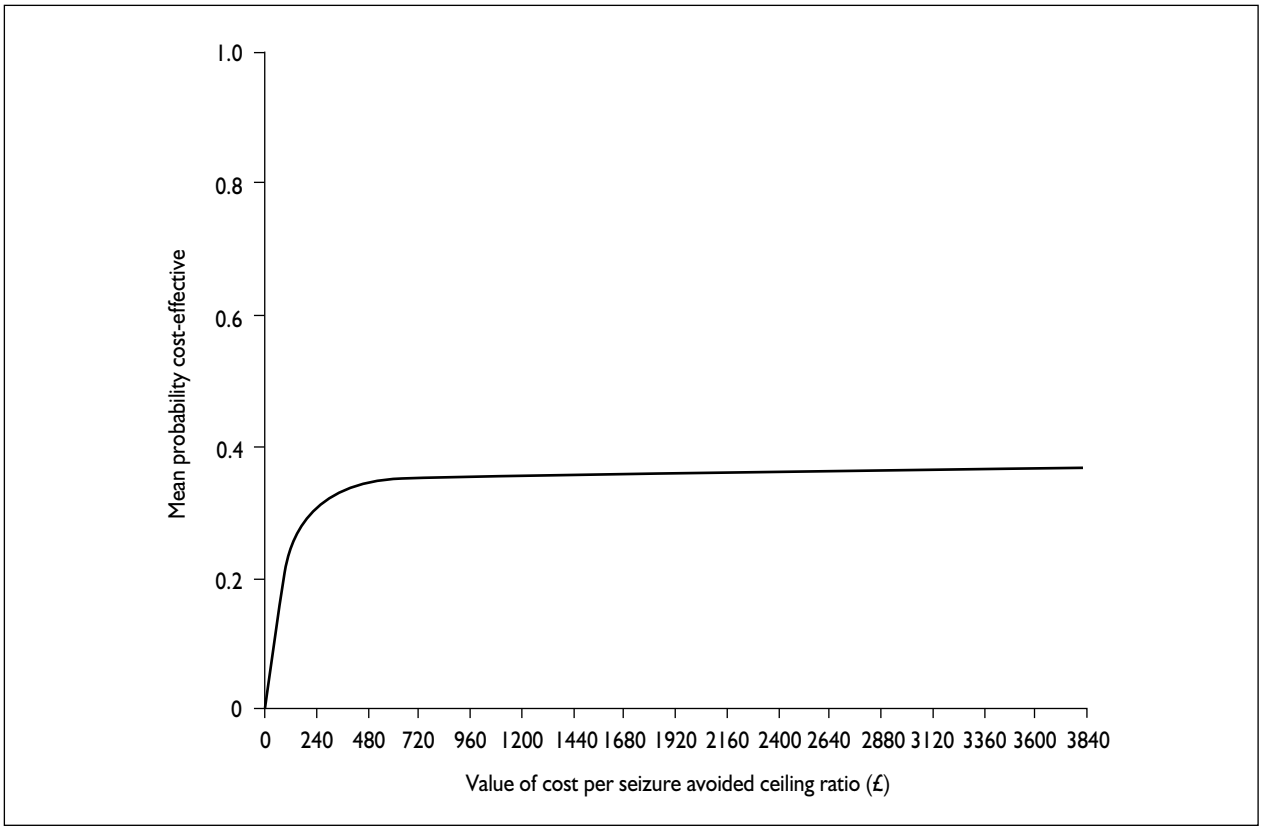


FIGURE 37 *CEAC for TPM relative to CBZ*

Arm B: valproate as standard drug

The first patient was randomised into the study on 12 January 1999 and randomisation continued up to 31 August 2004. Attempts were made to follow up all patients to, at the latest, a point in time between 1 May 2005 and 31 August 2005, although some follow-up data were collected up 13 January 2006. In total, 716 patients were randomised (*Table 47*). For Arm B, the numbers randomised to LTG, TPM, VPS appear balanced across stratification factors (centre, sex and clinical history) for the recruitment period 12 January 1999 to 31 August 2004.

During the course of the study, a number of patients withdrew from Arm B. The reasons for withdrawal and death are described in *Tables 47* and *48*.

A summary of baseline characteristics is given in *Table 49*, which shows that randomisation provided well-balanced treatment groups in the two arms.

The majority of patients randomised into Arm B were those with definite idiopathic generalised epilepsy (63%) or were unclassified (27%). Thus Arm B met the aim of being a pragmatic trial comparing drugs believed to have a broader spectrum of efficacy that included generalised onset seizures. It is notable that the ratio of male to female subjects indicates that there may have been some reluctance on the part of clinicians to randomise younger women to Arm B, where they might have been randomised to valproate. Patient disposition in the study is described in *Figure 38*.

Arm B achieved a relatively complete follow-up. When the 32 patients withdrawn from study and 11 patients who died are excluded from the following calculations, and follow-up data received after 31 August 2005 are truncated at 31 August 2005, overall, 2333 years of follow-up were achieved compared with 2504 years that could be expected. The overall percentage of follow-up achieved is 93% (*Table 50*).

One of the two primary outcomes for the study was the failure of the randomised drug as judged by its withdrawal or the addition of another AED. The number of patients withdrawing from randomised drug and/or having new AED added and/or withdrawing from study are presented in *Table 51*. The reason for drug withdrawal or addition or study withdrawal is defined as the earliest event for the purposes of these tables.

Because of the pragmatic nature of the trial design and the absence of blinding, it is important to understand the dosing of drugs used by clinicians and consider the degree to which the full dose ranges were explored before treatment failure events. These data are presented in *Table 52*.

There is satisfactory evidence that clinicians did explore a full dosing range before accepting treatment failure because of ISC. As would be expected, doses associated with UAEs were consistently lower than those associated with ISC. Patients achieving remission did so with low doses of randomised drug.

The majority (62%) of patients randomised to this arm of the study had a diagnosis of an idiopathic

TABLE 47 *Withdrawals [n (%)] from further follow-up (withdrawal from study) for Arm B*

Reason for withdrawal from study	LTG (*n* = 239)	TPM (*n* = 239)	VPS (*n* = 238)	Total (*n* = 716)
Consent withdrawn	5 (2.1)	7 (2.9)	4 (1.7)	16 (2.2)
Not epilepsy	4 (1.7)	6 (2.5)	4 (1.7)	14 (2.0)
Other reasons[a]	0	0	2 (0.8)	2 (0.3)

[a] 1 patient returned to live abroad, 1 patient was non-compliant and had emotional/psychological problems.

TABLE 48 *Summary of deaths by treatment group for Arm B*

Deaths	LTG (*n* = 239)	TPM (*n* = 239)	VPS (*n* = 238)	Total (*n* = 716)
Epilepsy related	1	0	1	2
Non-epilepsy related	3	3	3	9
Total, *n* (%)	4 (1.7)	3 (1.3)	4 (1.7)	11 (1.5)

TABLE 49 *Baseline demographic and clinical characteristics for Arm B*

	LTG (*n* = 239)	TPM (*n* = 239)	VPS (*n* = 238)	Total (*n* = 716)
Sex, *n* (%)				
Male	142 (59)	142 (59)	143 (60)	427 (60)
Female	97 (41)	97 (41)	95 (40)	289 (40)
Treatment history, *n* (%)				
Untreated	210 (87.9)	209 (87.5)	209 (87.8)	628 (87.7)
Monotherapy (not optimally treated)	19 (8.0)	20 (8.4)	21 (8.8)	60 (8.4)
Recent seizures after remission	10 (4.2)	10 (4.2)	8 (3.4)	28 (3.9)
History, *n* (%)				
Learning disability	24 (10.0)	26 (10.9)	19 (8.0)	69 (9.6)
Neurological deficit	5 (2.1)	3 (1.3)	8 (3.4)	16 (2.2)
Neurological disorder, *n* (%)				
Stroke/cerebrovascular	0 (0)	0 (0)	1 (0.4)	1 (0.1)
Intracranial surgery	1 (0.4)	0 (0)	2 (0.8)	3 (0.4)
Head injury	3 (1.3)	2 (0.8)	6 (2.5)	11 (1.5)
Meningitis/encephalitis	6 (2.5)	3 (1.3)	1 (0.4)	10 (1.4)
Other	12 (5.0)	9 (3.8)	8 (3.4)	29 (4.1)
History of seizures, *n* (%)				
Febrile convulsions	16 (6.7)	22 (9.2)	21 (8.8)	59 (8.2)
Any other acute symptomatic seizures	9 (3.8)	6 (2.5)	6 (2.5)	21 (2.9)
Epilepsy in first-degree relatives	53 (22.2)	38 (15.9)	38 (16.0)	129 (18.0)
Epilepsy syndrome, *n* (%)[a]				
Idiopathic partial	1 (0.4)	2 (0.8)	0 (0)	3 (0.4)
Symptomatic or cryptogenic partial	18 (7.5)	11 (4.6)	20 (8.4)	49 (6.9)
Idiopathic generalised	145 (60.7)	151 (63.5)	154 (64.7)	450 (62.9)
Other syndrome	9 (3.8)	8 (3.4)	5 (2.1)	22 (3.1)
Unclassified	66 (27.6)	66 (27.7)	59 (24.8)	191 (26.7)
Median interval between 1st and most recent seizure (25th, 75th centile), days	492 (162, 1510)	401 (105, 1702)	384 (126, 1402)	414 (128, 1561)
Median interval between most recent seizure and randomisation (25th, 75th centile), days	11 (1, 49)	13 (2, 41)	13 (1, 42)	13 (1.5, 44)
Median number of seizures (25th, 75th centile)	10 (3, 101)	8 (3, 100)	8.5 (3, 100)	8 (3, 100)
Mean age at first seizure ± SD (years)	17.5 ± 12.1	17.6 ± 11.5	18.3 ± 13.7	17.8 ± 12.5
Mean age ± SD (years)	22.8 ± 14.3	22.3 ± 13.3	22.5 ± 14.5	22.5 ± 14.0

[a] Missing data for epilepsy syndrome for 1 individual on TPM.

TABLE 50 *Completeness of follow-up for Arm B*

Follow-up (years)	LTG (*n* = 226)	TPM (*n* = 223)	VPS (*n* = 224)	Total (*n* = 673)
Actual	778	768	787	2333
Expected	839	831	834	2504
Actual/expected (%)	93	92	94	93
Median (min., max.)	3.5 (0, 6.6)	3.5 (0, 6.4)	3.5 (0.6, 6.4)	3.5 (0, 6.6)

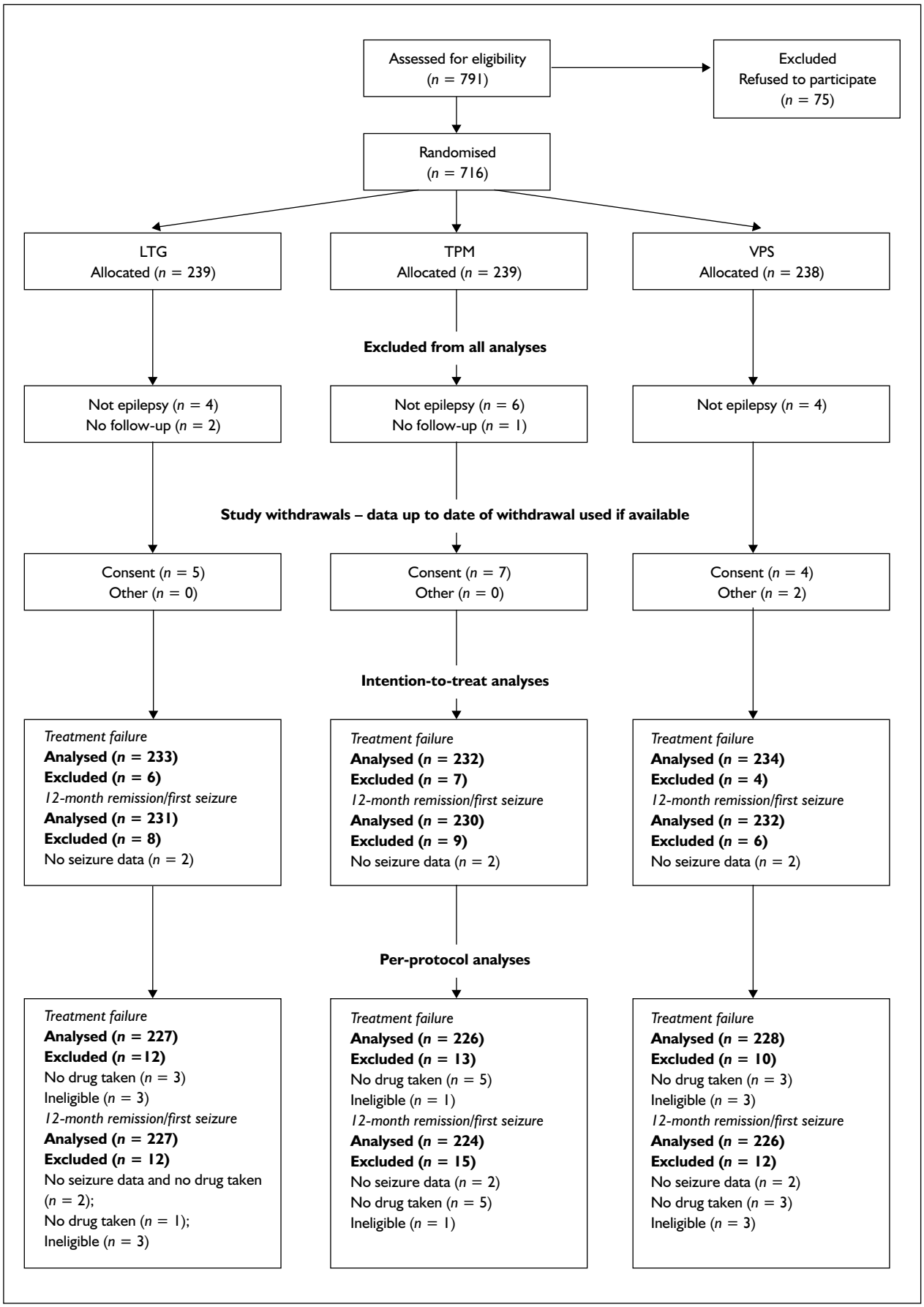


FIGURE 38 *Patient disposition for Arm B*

TABLE 51 *Reasons for treatment termination for Arm B: numbers in table are number of patients with percentages in parentheses*

Reason for termination	LTG[a] (*n* = 237)	TPM[a] (*n* = 238)	VPS (*n* = 238)	Total (*n* = 713)
Treatment failure[b]				
ISC	53 (22.4)	28 (11.8)	21 (8.8)	102 (14.3)
UAE	25 (10.5)	57 (23.9)	35 (14.7)	117 (16.4)
ISC and UAE[c]	7 (3.0)	18 (7.6)	11 (4.6)	36 (5.0)
Non-compliance	3 (1.3)	0 (0)	0 (0)	3 (0.4)
Epilepsy-related death	1 (0.4)	0 (0)	1 (0.4)	2 (0.3)
Perceived adverse event	0 (0)	3 (1.3)	1 (0.4)	4 (0.6)
Pregnancy	2 (0.8)	3 (1.3)	4 (1.7)	9 (1.3)
Patient decision	2 (0.8)	1 (0.4)	2 (0.8)	5 (0.7)
Perceived remission[d]	7 (3.0)	6 (2.5)	10 (4.2)	23 (3.2)
Unknown	1 (0.4)	1 (0.4)	0 (0)	2 (0.3)
Total number of treatment failures	101 (43)	117 (49)	85 (36)	303 (42)
Non treatment failure[e]				
Consent withdrawn	4 (1.7)	3 (1.3)	3 (1.3)	10 (1.4)
Non-epilepsy-related death	1 (0.4)	2 (0.8)	3 (1.3)	6 (0.8)
Lost to follow-up	0 (0)	0 (0)	1 (0.4)	1 (0.1)
Not epilepsy	3 (1.3)	3 (1.3)	3 (1.3)	9 (1.3)
Other	2 (0.8)	4 (1.7)	0 (0)	6 (0.8)
Remission of epilepsy	17 (7.2)	25 (10.5)	46 (19.3)	88 (12.3)
Total number of non-treatment failure withdrawals	27 (11)	37 (16)	56 (24)	120 (17)
Still on drug at end of study	109 (46)	84 (35)	97 (41)	290 (41)

[a] No follow-up data for 2 individuals on LTG and 1 individual on TPM.
[b] Withdrawn from randomised drug/study/other drug added for bad reason and counted as event in time to treatment failure analysis.
[c] Treated as ISC in competing risks analyses.
[d] Period in remission is less than 12 months.
[e] Censored at date of termination in time to treatment failure analysis.

TABLE 52 *Arm B – dose, as mean (standard deviation) range, at withdrawal or last follow-up (excluding not epilepsy and children, entire recruitment period)*[a]

Reason for withdrawal	LTG	TPM	VPS
ISC	*n* = 24 341 (169) 75–600	*n* = 3 367 (225) 150–600	*n* = 9 1600 (896) 500–3000
UAE	*n* = 9 119 (99) 25–300	*n* = 23 172 (110) 50–500	*n* = 13 838 (240) 500–1200
ISC and UAE	*n* = 2 200 (0) 200–200	*n* = 11 177 (109) 50–400	*n* = 8 1325 (568) 700–2000
Other reason for withdrawal	*n* = 10 150 (47) 50–200	*n* = 8 169 (53) 100–250	*n* = 12 958 (462) 400–2000
Remission of seizures	*n* = 5 120 (45) 100–200	*n* = 5 130 (27) 100–150	*n* = 9 944 (336) 200–1500
Still on randomised drug	*n* = 77 203 (101) 50–500	*n* = 63 171 (86) 25–400	*n* = 72 1081 (463) 300–3000

[a] Dose data are missing for a number of patients. For this subset of patients with missing dose data, time to withdrawal tends to be shorter and reason for withdrawal more likely to be UAE or other reasons compared with those we have dose data for. Dose data in this table should be interpreted with this in mind.

generalised epilepsy at randomisation (*Table 49*). The numbers of patients with specific subtypes of idiopathic generalised epilepsy is described in *Table 53*.

The distribution of age at randomisation of subjects with idiopathic generalised epilepsy is illustrated in *Figure 39*. For these age-related syndromes, age at randomisation is appropriate for diagnosis. Some older patients with idiopathic generalised epilepsy were randomised, but a number of these were individuals previously treated with what may have been inappropriate monotherapies or individuals with a previous history of epilepsy who had relapsed after a period of remission.

Time to treatment failure

Because time to treatment failure is a global outcome measure, further analysis of this outcome was undertaken to assess the contributions from tolerability on the one hand and seizure control on the other. A frequency plot is shown in *Figure 40*. From *Table 51*, it can be seen that reasons for treatment failure do vary between drugs.

TABLE 53 *Subtypes of idiopathic generalised epilepsy*

Syndrome	Drug to which randomised, *N* (%)			Total
	LTG	TPM	VPS	
Childhood absence	21 (14)	20 (13)	25 (16)	66 (15)
Juvenile absence	20 (14)	14 (9)	11 (7)	45 (10)
Juvenile myoclonic	39 (27)	41 (27)	39 (25)	119 (26)
Epilepsy with tonic–clonic seizures on awakening	14 (10)	15 (10)	13 (8)	42 (9)
Other idiopathic generalised epilepsy not specified	50 (34)	56 (37)	62 (40)	168 (37)
Childhood absence + other idiopathic generalised epilepsy not specified	1 (1)	0	0	1 (0)
Childhood absence + epilepsy with tonic–clonic seizures on awakening	0	1 (1)	0	1 (0)
Other epilepsy syndrome	0	4 (3)	4 (3)	8 (2)
Total	145	151	154	450

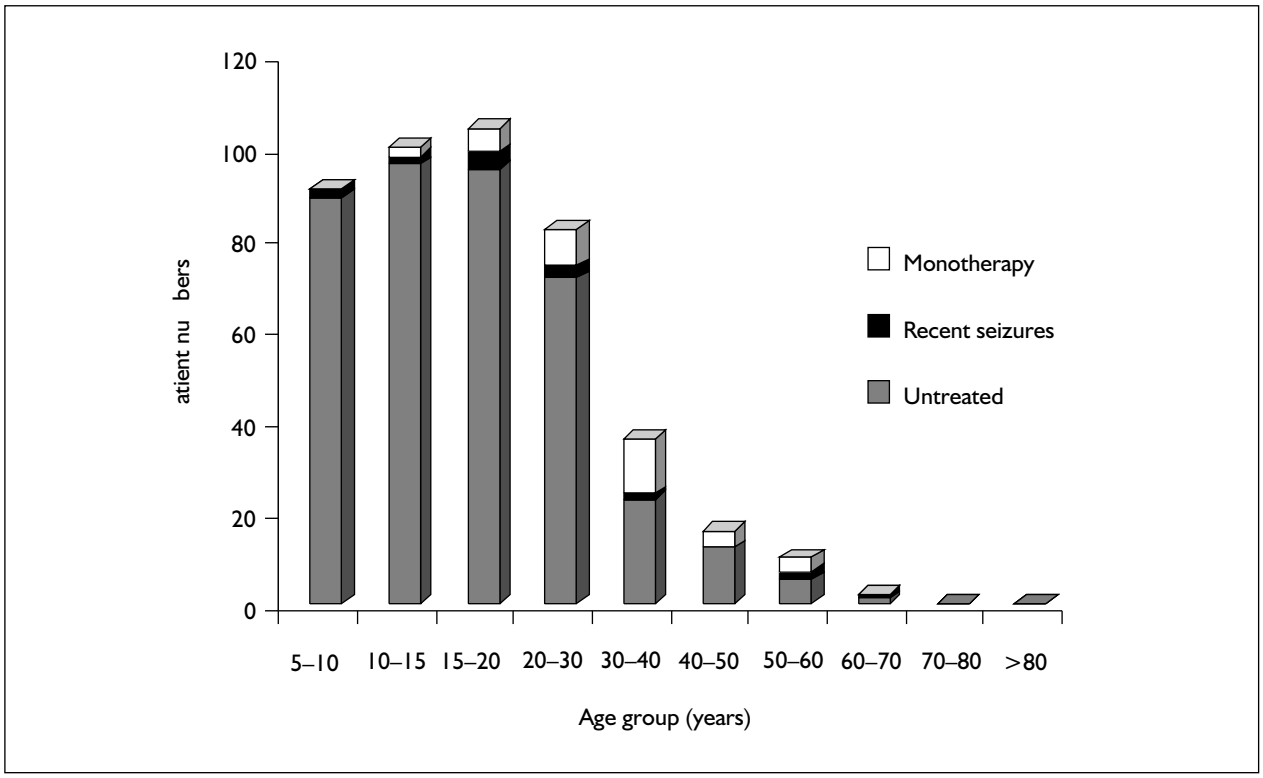


FIGURE 39 *Age range and treatment history at randomisation – Arm B*

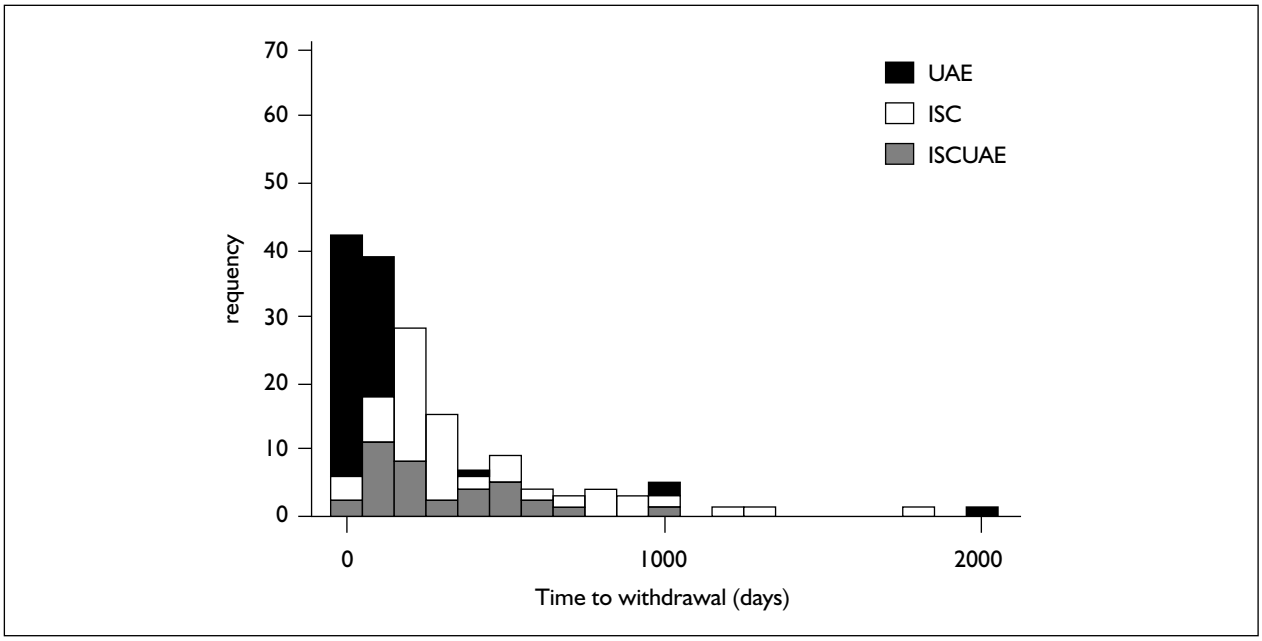


FIGURE 40 *Distribution of time to withdrawal for inadequate seizure control (ISC), unacceptable adverse events (UAEs) and ISC plus UAE (ISCUAE) (see* Table 47*)*

Again, there is evidence that treatment failure due to unacceptable side-effects occurs earlier after randomisation than does treatment failure for ISC, making analysis of competing risks important.

Results are presented in *Figures 41–44* with comparisons of pair-wise HRs, and absolute differences in probabilities between VPS and comparator drugs. Contributions to treatment failure from UAEs and ISC are summarised.

These analyses show that there are statistically significant differences between drugs for time to treatment failure for any reason and that VPS is the best option. Pair-wise comparisons show that it is statistically superior to TPM, the least favoured option, with LTG intermediate. Cumulative risk analysis of withdrawal for UAEs and ISC indicates that LTG is least likely to be associated with UAEs, and TPM most likely. HRs for TPM indicate that it is statistically inferior to both VPS and LTG for failure due to UAEs. However LTG is most likely to be associated with treatment failure due to ISC, with VPS least likely. LTG HRs indicate that it is twice as likely to fail because of ISC than VPS, a difference that is significant.

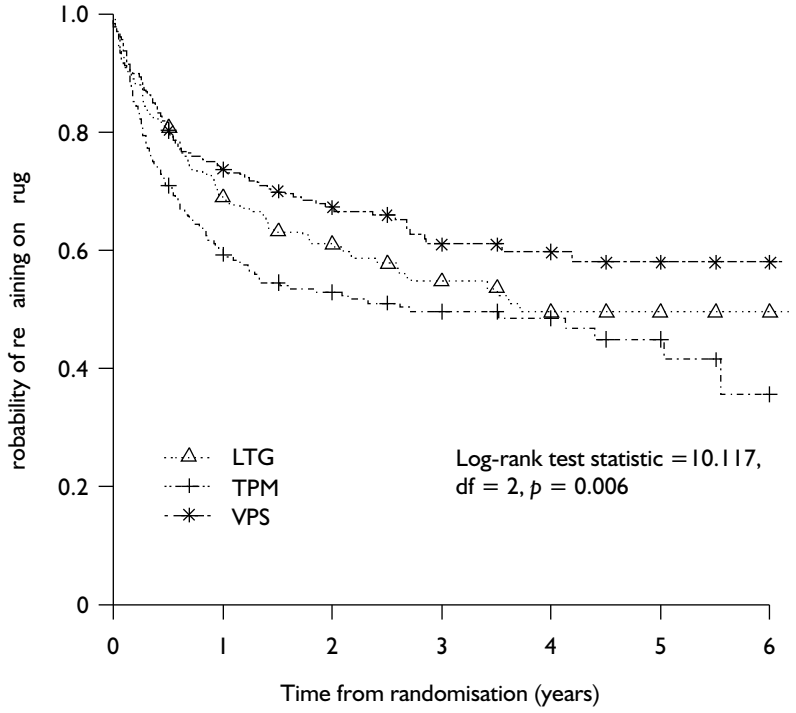
It is also notable that when the analyses are restricted to patients who at the time of randomisation were identified as having a generalised epilepsy syndrome, the superiority of VPS for time to treatment failure appears more marked and that it is significantly superior to both TPM and LTG for this outcome.

Time to 12-month remission

Results for this outcome are presented in *Figures 45–47* with both ITT and PP analyses.

Again, the drugs are significantly different for achievement of 12-month remission, with a high proportion (>80% by 4 years) of subjects achieving 1-year remission. Pair-wise comparisons for the ITT analysis indicate that VPS is the preferred option and is statistically superior to LTG. TPM appears intermediate between the two. It is notable, however, that the survival curves for TPM and VPS overlap from a point approximately 700 days after randomisation. Again, the difference between VPS and comparator drugs is larger when this is restricted to patients with idiopathic generalised epilepsy.

Because ITT analysis includes seizure data after treatment failure events, a PP analysis was undertaken. This confirms the superiority of VPS over LTG and TPM for time to 12-month remission, which achieves significance in both cases. The comparisons between the ITT and PP analyses appear to indicate that the similarity for the outcome between VPS and TPM for the ITT analysis is likely to be due to subjects experiencing treatment failure on TPM being switched to VPS.

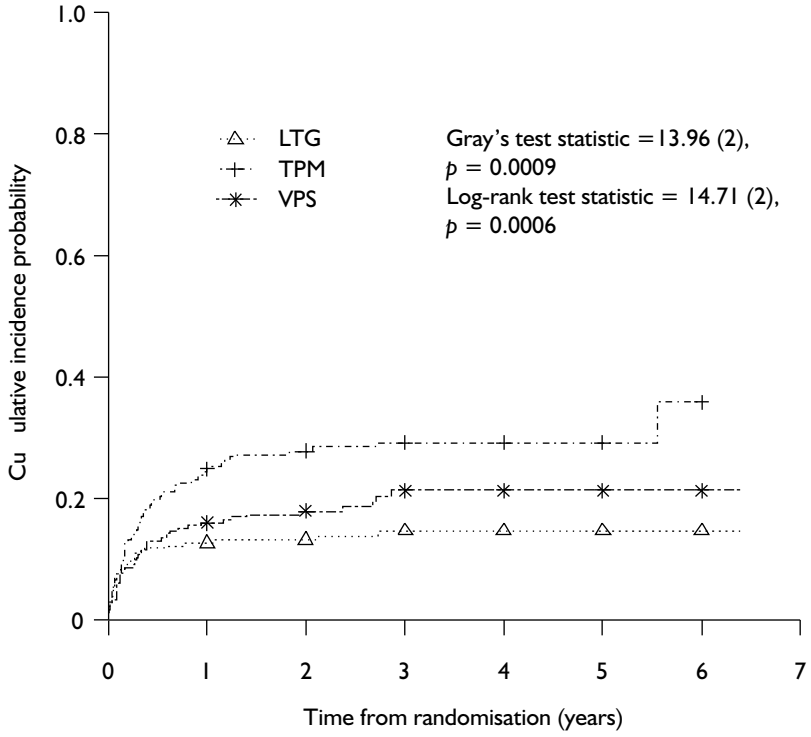


Drug (events/ total)		Year					
		1	2	3	4	5	6
VPS (84/234)	Number at risk	165	114	61	40	14	4
	% still on drug (95% CI)	74 (68 to 79)	67 (61 to 73)	61 (54 to 68)	60 (52 to 67)	58 (50 to 66)	58 (50 to 66)
LTG (100/233)	Number at risk	152	106	60	29	10	3
	Difference in % still on drug compared with VPS (95% CI)	–5 (–13 to 3)	–6 (–15 to 3)	–6 (–16 to 4)	–10 (–21 to 1)	–8 (–20 to 3)	–8 (20 to 3)
TPM (115/232)	Number at risk	129	91	55	35	13	1
	Difference in % still on drug compared with VPS (95% CI)	–14 (–23 to –6)	–14 (–23 to –5)	–11 (–21 to –2)	–11 (–21 to –1)	–13 (–24 to –2)	–16 (–29 to –4)

HR[a] (95% CI)	Baseline drug		
	VPS	LTG	TPM
VPS	–	0.80 (0.60 to 1.07)	*0.64 (0.48 to 0.84)*
LTG	1.25 (0.94 to 1.68)	–	0.80 (0.61 to 1.04)
TPM	*1.57 (1.19 to 2.08)*	1.25 (0.96 to 1.64)	–

[a] HR > 1 indicates that failure occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 41 *Time to treatment failure (Arm B) for entire recruitment period*

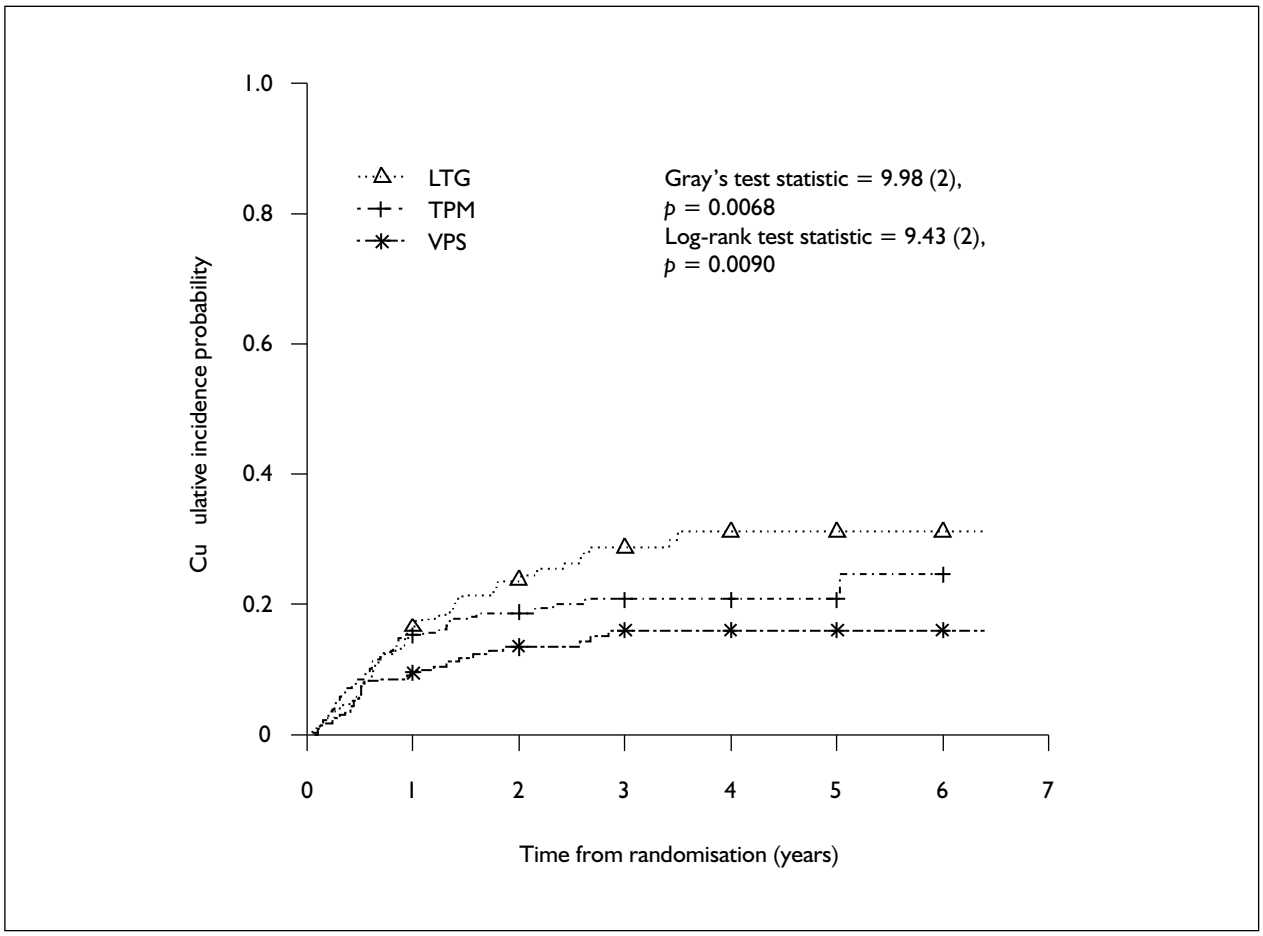


Drug (events/ total)		Year					
		1	**2**	**3**	**4**	**5**	**6**
VPS (45/234)	% still on drug (95% CI)	84 (79 to 89)	82 (77 to 87)	79 (73 to 85)	79 (73 to 85)	79 (73 to 85)	79 (73 to 85)
LTG (32/233)	Difference in % still on drug compared with VPS (95% CI)	3 (–3 to 10)	5 (–2 to 11)	7 (–1 to 14)	7 (–1, 14)	7 (–1 to 14)	7 (–1 to 14)
TPM (65/232)		–9 (–16 to –1)	–10 (–18 to –2)	–8 (–16 to 1)	–8 (–16 to 1)	–8 (–16 to 1)	–14 (–30 to 1)

HR[a] (95% CI)	**Baseline drug**		
	VPS	**LTG**	**TPM**
VPS	–	1.39 (0.88 to 2.19)	*0.64 (0.44 to 0.94)*
LTG	0.72 (0.46 to 1.14)	–	*0.46 (0.30 to 0.71)*
TPM	*1.55 (1.07 to 2.26)*	*2.15 (1.41 to 3.30)*	–

[a] HR > 1 indicates that failure occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 42 *Time to treatment failure (Arm B) for entire recruitment period – cumulative incidence for UAE (ISC + UAE counted as ISC)*

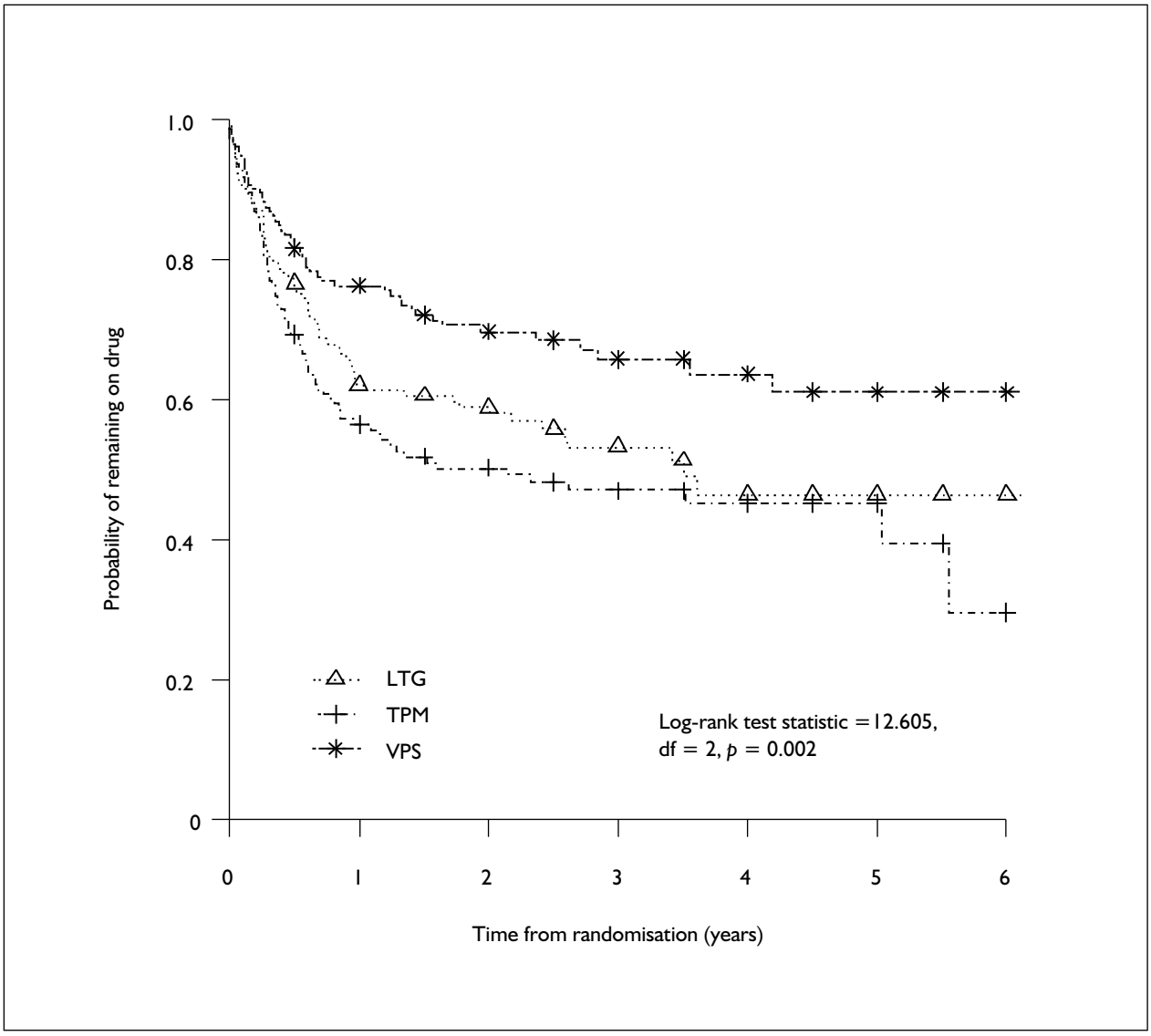


Drug (events/ total)		Year					
		1	2	3	4	5	6
VPS (33/234)	% still on drug (95% CI)	90 (87 to 94)	87 (82 to 91)	84 (79 to 89)	84 (79 to 89)	84 (79 to 89)	84 (79 to 89)
LTG (60/233)	Difference in % still on drug compared with VPS (95% CI)	–7 (–13 to –1)	–10 (–17 to –3)	–13 (–21 to –4)	–15 (–24 to –6)	–15 (–24 to –6)	–15 (–24 to –6)
TPM (45/232)		–6 (–12 to 0)	–5 (–12 to 2)	–5 (–12 to 3)	–5 (–12 to 3)	–5 (–12 to 3)	–9 (–19 to 2)

HR[a] (95% CI)	Baseline drug		
	VPS	LTG	TPM
VPS	–	*0.51 (0.34 to 0.78)*	0.69 (0.44 to 1.09)
LTG	*1.95 (1.28 to 2.98)*	–	1.35 (0.92 to 1.99)
TPM	1.45 (0.92 to 2.27)	0.74 (0.50 to 1.09)	–

[a] HR > 1 indicates that failure occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 43 *Time to treatment failure (Arm B) for entire recruitment period – cumulative incidence for ISC (ISC + UAE counted as ISC)*

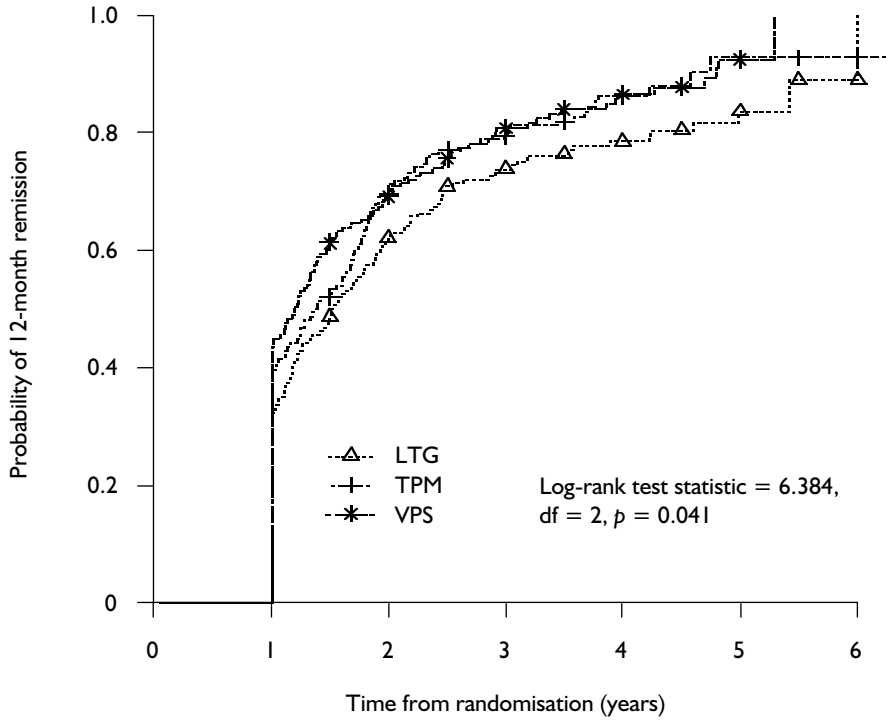


Drug	Events	Total
LTG	65	141
TPM	76	147
VPS	50	152
Total	191	440

HR[a] (95% CI)	Baseline drug		
	VPS	LTG	TPM
VPS	–	*0.65 (0.45 to 0.93)*	*0.53 (0.37 to 0.76)*
LTG	*1.55 (1.07 to 2.24)*	–	0.82 (0.59 to 1.14)
TPM	*1.89 (1.32 to 2.70)*	1.22 (0.88 to 1.70)	–

[a] HR > 1 indicates that failure occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 44 *Time to treatment failure for entire recruitment period (Arm B, generalised syndrome only)*

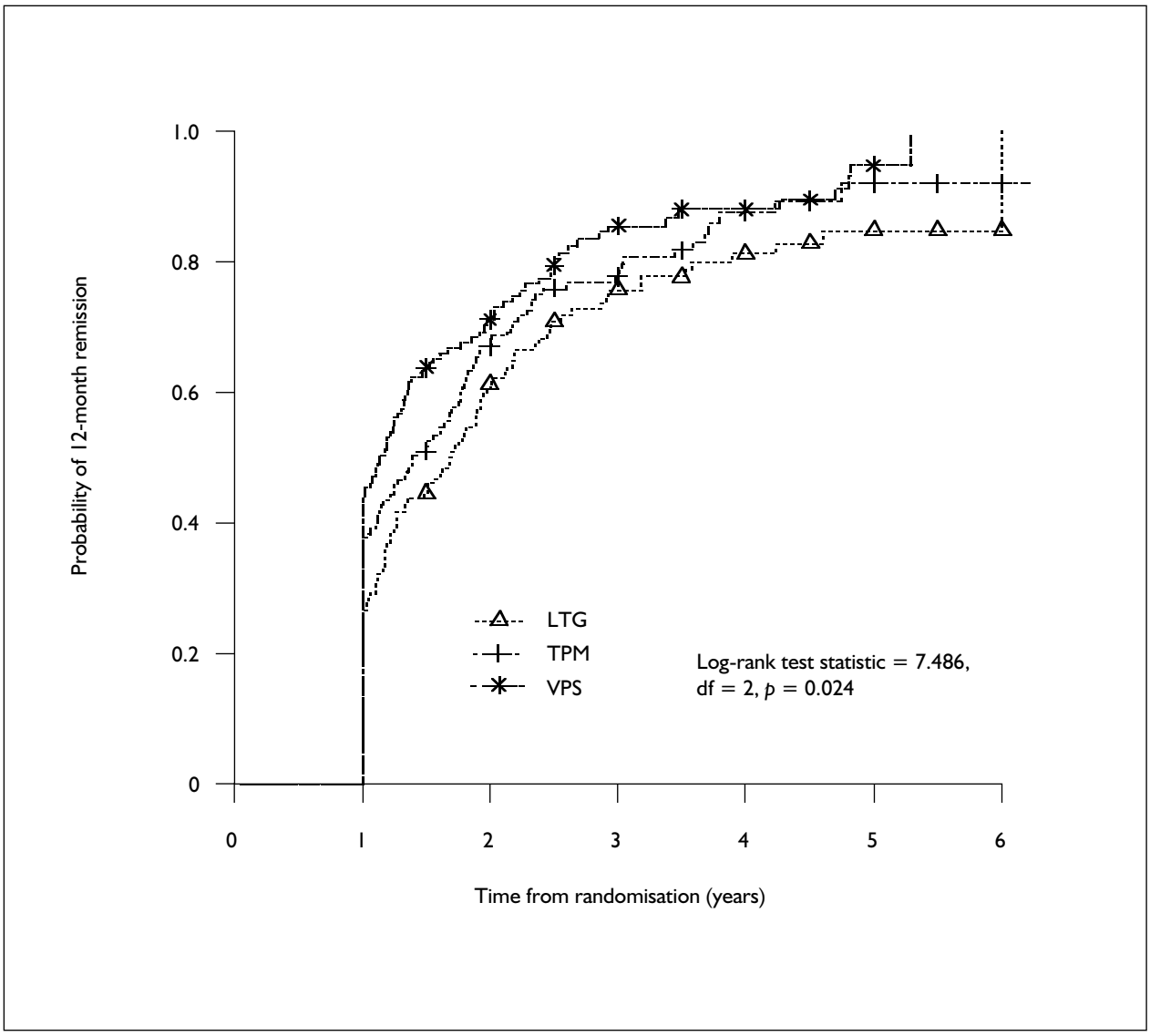


Drug (events/ total)		Year				
		1	2	3	4	5
VPS (180/232)	Number at risk	221	54	28	15	4
	% 12-month remission (95% CI)	43 (37 to 50)	69 (63 to 76)	81 (75 to 87)	87 (81 to 92)	92 (87 to 98)
LTG (168/231)	Number at risk	222	74	43	25	8
	Difference in % 12-month remission compared with VPS (95% CI)	–11 (–20 to –2)	–7 (–16 to 2)	–7 (–15 to 1)	–8 (–16 to 0)	–9 (–17 to 0)
TPM (178/230)	Number at risk	219	59	32	14	2
	Difference in % 12-month remission compared with VPS (95% CI)	–4 (–13 to 5)	0 (–9 to 9)	–1 (–9 to 7)	0 (–8 to 7)	0 (–8 to 9)

HR[a] (95% CI)	Baseline drug		
	VPS	LTG	TPM
VPS	–	*1.31 (1.06 to 1.62)*	1.07 (0.87 to 1.32)
LTG	*0.76 (0.62 to 0.94)*	–	0.82 (0.66 to 1.01)
TPM	0.93 (0.76 to 1.15)	1.23 (0.99 to 1.51)	–

[a] HR > 1 indicates that 12 month remission occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 45 *Time to 12-month remission (Arm B)*

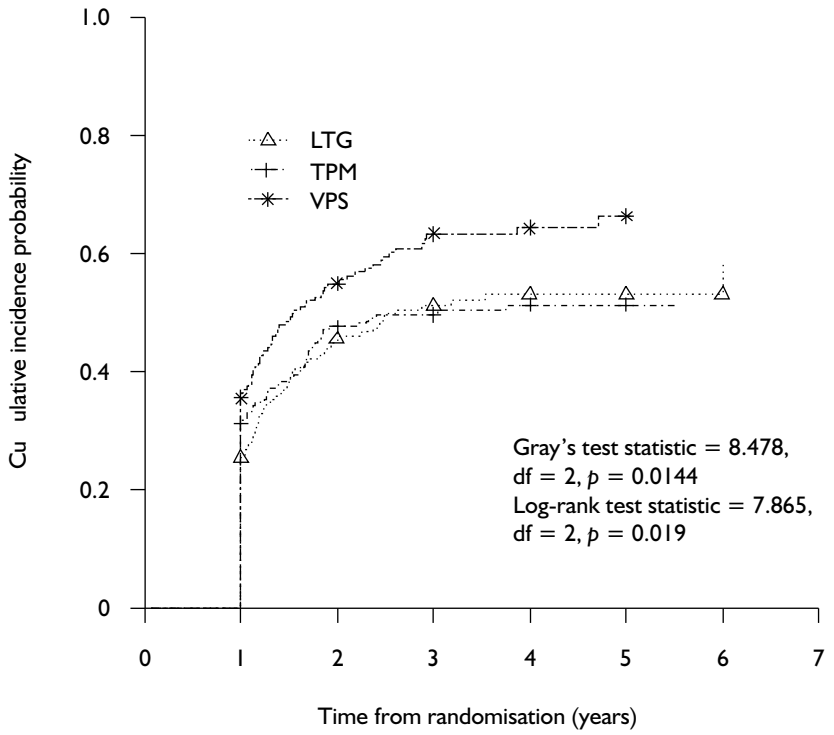


Drug	Events	Total
LTG	105	141
TPM	114	145
VPS	124	152
Total	343	438

HR[a] (95% CI)	Baseline drug		
	VPS	LTG	TPM
VPS	–	*1.47 (1.13 to 1.90)*	1.22 (0.94 to 1.57)
LTG	*0.68 (0.53 to 0.89)*	–	0.83 (0.64 to 1.08)
TPM	0.82 (0.64 to 1.06)	1.21 (0.93 to 1.57)	–

[a] HR > 1 indicates that 12-month remission occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 46 *Time to 12-month remission (Arm B, generalised syndromes only)*



Drug (events/ total)		Year				
		1	2	3	4	5
VPS (129/226)	Number at risk	161	25	6	4	1
	% 12-month remission (95% CI)	36 (29 to 42)	55 (48 to 62)	63 (57 to 70)	64 (57 to 71)	66 (59 to 74)
LTG (105/227)	Number at risk	151	34	12	4	1
	Difference in % 12-month remission compared with VPS (95% CI)	–10 (–19 to –1)	–9 (–19 to 0)	–12 (–22 to –2)	–11 (–21 to –1)	–13 (–24 to –3)
TPM (104/224)	Number at risk	127	16	8	3	1
	Difference in % 12-month remission compared with VPS (95% CI)	–4 (–13 to 5)	–7 (–17 to 2)	–14 (–23 to –4)	–13 (–23 to –3)	–15 (–25 to –5)

HR[a] (95% CI)	Baseline drug		
	VPS	LTG	TPM
VPS	–	*1.32 (1.05 to 1.29)*	*1.31 (1.04 to 1.65)*
LTG	*0.76 (0.60 to 0.95)*	–	0.99 (0.77 to 1.27)
TPM	*0.77 (0.61 to 0.97)*	1.01 (0.79 to 1.29)	–

[a] HR > 1 indicates that 12-month remission occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 47 *Time to 12-month remission (Arm B), PP analysis*

TABLE 54 *Arm B – summary of treatment taken when 12-month remission achieved*[a]

Randomised drug	LTG	TPM	VPS	CBZ	ETH	LVT	PHT	TGB	Polytherapy	Total
LTG	111 (71.6)	4 (2.6)	29 (18.7)	1 (0.6)	0	2 (1.3)	0	0	8 (5.1)	155[b] (100)
TPM	9 (5.6)	107 (66.0)	34 (21.0)	1 (0.6)	4 (2.5)	0	0	0	7 (4.2)	162[c] (100)
VPS	15 (9.3)	0	133 (82.6)	4 (2.5)	3 (1.9)	0	1 (0.6)	1 (0.6)	4 (2.5)	161[d] (100)

ETH, ethosuximide; LVT, levetiracetam; PHT, phenytoin; TGB, tigabine.
[a] Randomised drug if date of withdrawal occurred after date of 12-month remission and drug listed at visit prior to date of 12-month remission otherwise. If more than one drug listed at visit prior to date of 12-month remission, it may be possible that at the time of remission only one of the drugs was being taken. Data: *n* (%).
[b] No AED being taken or no information on AED at time of remission for 13 patients.
[c] No AED being taken or no information on AED at time of remission for 16 patients.
[d] No AED being taken or no information on AED at time of remission for 19 patients.

Table 54 describes the treatments leading to remission, including those that occurred after switching from the randomised drug.

Secondary clinical outcomes

Time to 24-month remission

This outcome is described in *Figures 48* and *49*, which illustrate both ITT and PP analyses.

Data for the clinically important 24-month outcome are consistent with those for the 12-month remission outcome. The PP analysis shows VPS to be statistically superior to both LTG and TPM.

Time to first seizure

Outcomes are described in *Figures 50–52* for ITT and PP analyses.

Analyses for time to first seizure show that the drugs differ, with VPS being the preferred option, LTG the poorest and TPM intermediate between the two but nevertheless significantly superior to LTG. VPS and TPM cannot be regarded as equivalent for this outcome because of the trend towards better outcome with the VPS and wide CLs in the PP analysis.

It is notable that for this efficacy outcome the differences between drugs appear larger for patients with definite generalised epilepsy syndromes than for all patients randomised to this arm of the study.

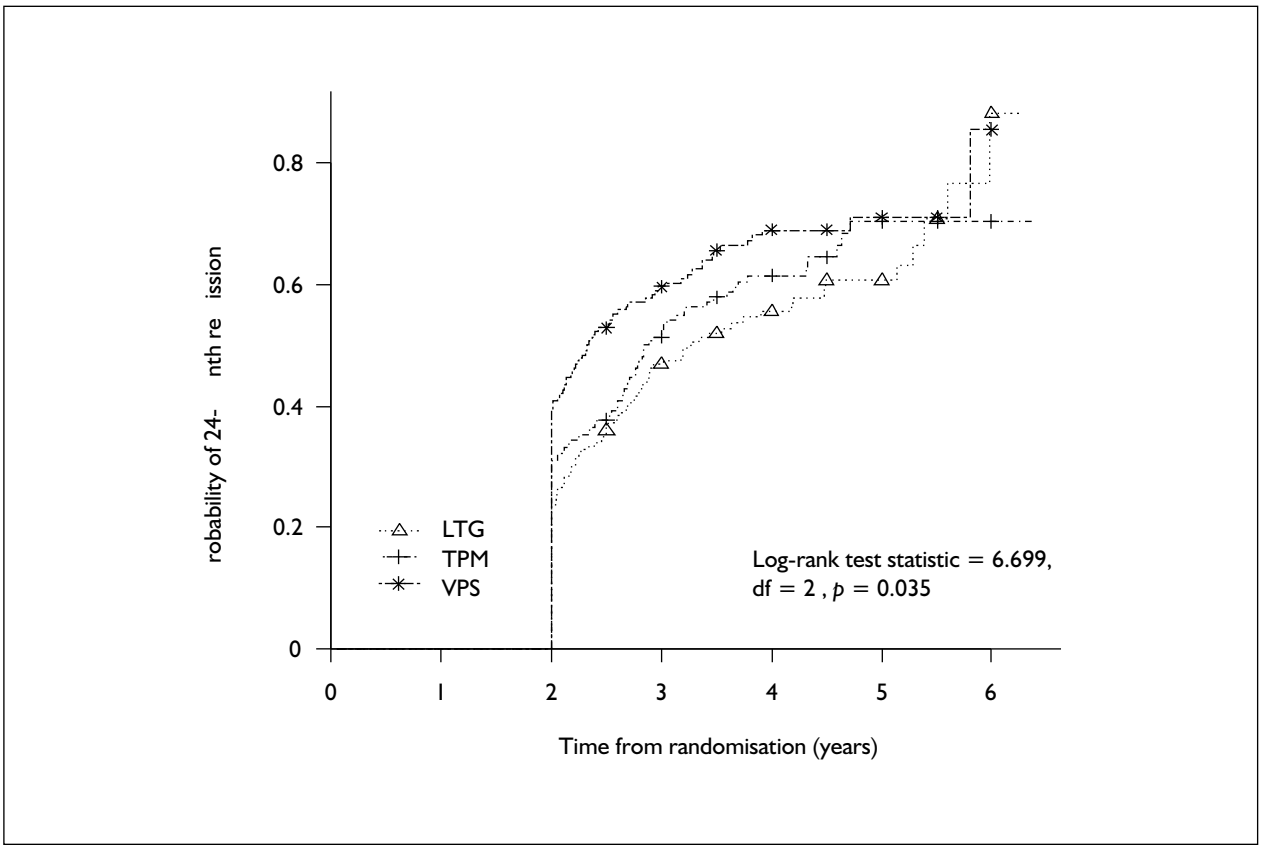
The PP analysis (where observations are censored for treatment failure) again confirms the superiority of VPS over TPM and LTG.

Effects of epilepsy syndrome

As noted for all analyses, the superiority of VPS over LTG and TPM appeared greater when analysis was restricted to patients classified as having idiopathic generalised epilepsy. This was further explored by testing for an interaction between treatment and syndrome. Comparisons of outcomes were made between the 441 patients with idiopathic generalised epilepsy, 186 unclassified patients and 52 classified as partial or other syndromes (numbers included in analyses may deviate from these if outcome data are not available).

There is no evidence of an interaction for the treatment failure outcomes (change in $-2\log L = 7.31$; 4 df; $p = 0.12$). There is however, some evidence of an interaction for purer efficacy outcomes. For 12-month remission the change in $-2\log L$ on adding syndrome by treatment interaction terms is 9.78 (4 df; $p = 0.04$) and for 24-month remission the change is 14.26 (4 df; $p = 0.007$). On adding interaction terms for time to first seizure, the change in $-2\log L$ is 17.62 (4 df; $p = 0.001$).

For the efficacy outcomes, results for the unclassified group suggest that VPS is best overall, although HRs indicate less extreme results in favour of VPS with wider CIs around HRs due to the smaller number of patients in this group (*Table 55*). Results for the partial/other syndromes group show a statistically significant benefit in favour of TPM, which is consistent across all efficacy outcomes.

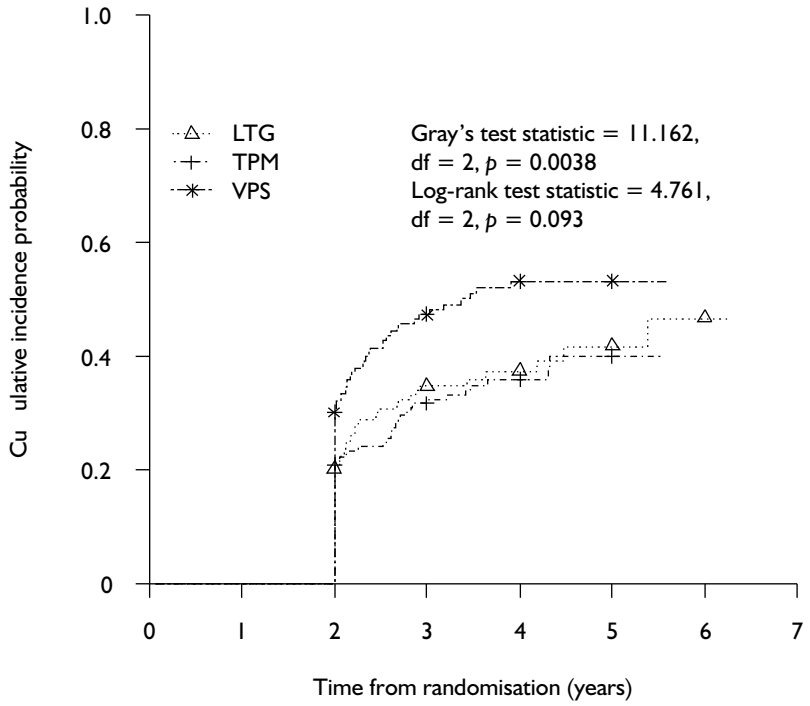


Drug (events/ total)		Year				
		1	2	3	4	5
VPS (124/232)	Number at risk	187	61	31	11	1
	% 24-month remission (95% CI)	39 (32 to 46)	60 (53 to 67)	69 (62 to 76)	71 (63 to 79)	86 (65 to 106)
LTG (102/231)	Number at risk	185	80	42	16	1
	Difference in % 24-month remission compared with VPS (95% CI)	–16 (–25 to –6)	–13 (–23 to –2)	–13 (–24 to –3)	–11 (–22 to 1)	3 (–24 to 30)
TPM (108/230)	Number at risk	183	71	34	10	3
	Difference in % 24-month remission compared with VPS (95% CI)	–8 (–18 to 1)	–8 (–19 to 2)	–8 (–18 to 3)	–1 (–13 to 11)	–15 (–37 to 7)

HR[a] (95% CI)	Baseline drug		
	VPS	LTG	TPM
VPS	–	*1.43 (1.10 to 1.86)*	1.26 (0.97 to 1.63)
LTG	*0.70 (0.54 to 0.91)*	–	0.88 (0.67 to 1.15)
TPM	0.80 (0.61 to 1.03)	1.14 (0.87 to 1.49)	–

[a] HR > 1 indicates that 24-month remission occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 48 *Time to 24-month remission (Arm B)*

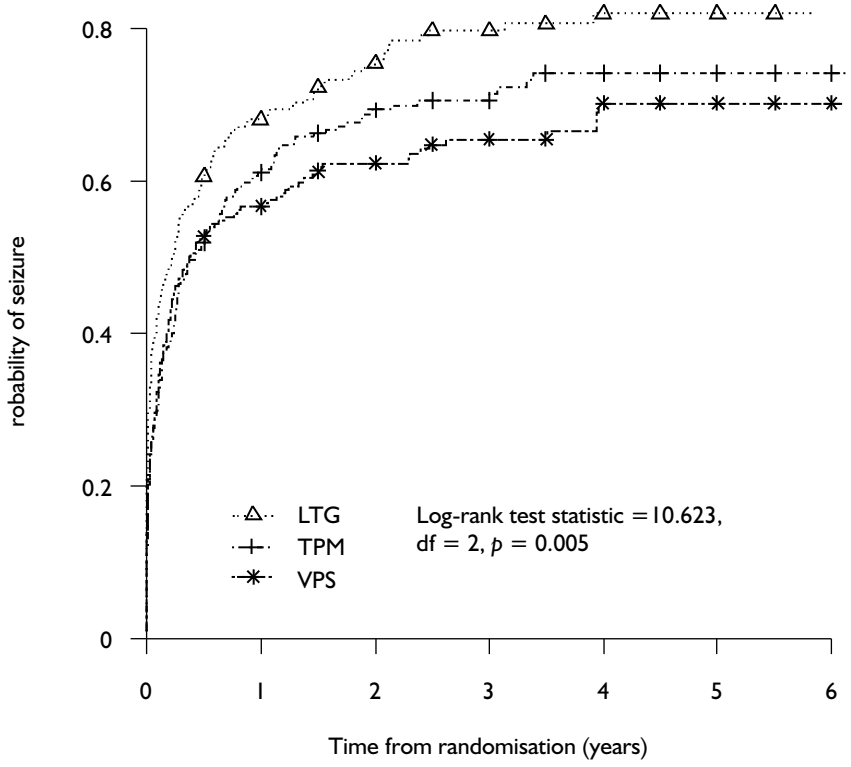


Drug (events/ total)		Year			
		2	**3**	**4**	**5**
VPS (79/226)	Number at risk	110	21	10	2
	% 24-month remission (95% CI)	30 (23 to 37)	47 (40 to 55)	53 (45 to 61)	53 (45 to 61)
LTG (59/227)	Number at risk	104	28	10	3
	Difference in % 24-month remission compared with VPS (95% CI)	–10 (–19 to –1)	–13 (–23 to –2)	–16 (–27 to –5)	–11 (–24 to 1)
TPM (58/224)	Number at risk	90	25	11	3
	Difference in % 24-month remission compared with VPS (95% CI)	–9 (–19 to 0)	–16 (–26 to –5)	–17 (–28 to –7)	–13 (–25 to –2)

HR[a] (95% CI)	**Baseline drug**		
	VPS	**LTG**	**TPM**
VPS	–	*1.45 (1.08 to 1.96)*	*1.53 (1.13 to 2.06)*
LTG	*0.69 (0.51 to 0.93)*	–	1.05 (0.76 to 1.46)
TPM	*0.65 (0.48 to 0.89)*	0.95 (0.69 to 1.32)	–

[a] HR > 1 indicates that 24-month remission occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 49 *Time to 24-month remission (Arm B) for entire recruitment period as PP analysis*

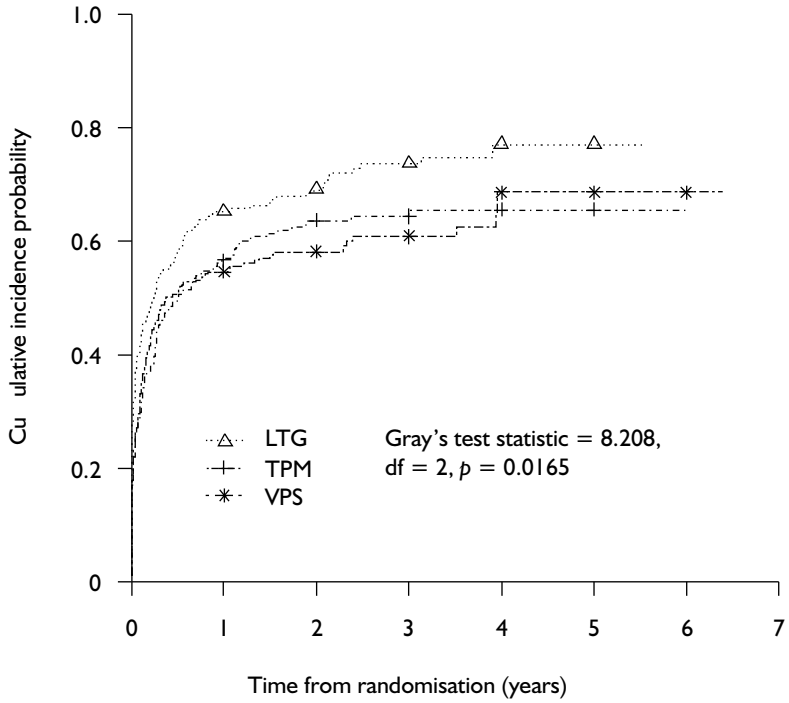


Drug (events/ total)		Year					
		1	2	3	4	5	6
VPS (152/232)	Number at risk	96	71	43	23	9	4
	% still on drug (95% CI)	57 (50 to 63)	62 (56 to 69)	66 (59 to 72)	70 (63 to 77)	70 (63 to 77)	70 (63 to 77)
LTG (181/231)	Number at risk	72	43	23	13	5	–
	Difference in % still on drug compared with VPS (95% CI)	11 (3 to 20)	13 (5 to 22)	14 (6 to 23)	12 (3 to 21)	12 (3 to 21)	–
TPM (163/230)	Number at risk	86	55	35	22	14	1
	Difference in % still on drug compared with VPS (95% CI)	4 (–5 to 13)	7 (–2 to 16)	5 (–4 to 14)	4 (–5 to 13)	4 (–5 to 13)	4 (–5 to 13)

HR[a] (95% CI)	Baseline drug		
	VPS	LTG	TPM
VPS	–	*0.71 (0.57 to 0.88)*	0.91 (0.73 to 1.14)
LTG	*1.41(1.14 to 1.75)*	–	*1.28 (1.04 to 1.59)*
TPM	1.10(0.88 to 1.37)	*0.78 (0.63 to 0.96)*	–

[a] HR > 1 indicates that first seizure occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 50 *Time to first seizure (Arm B)*

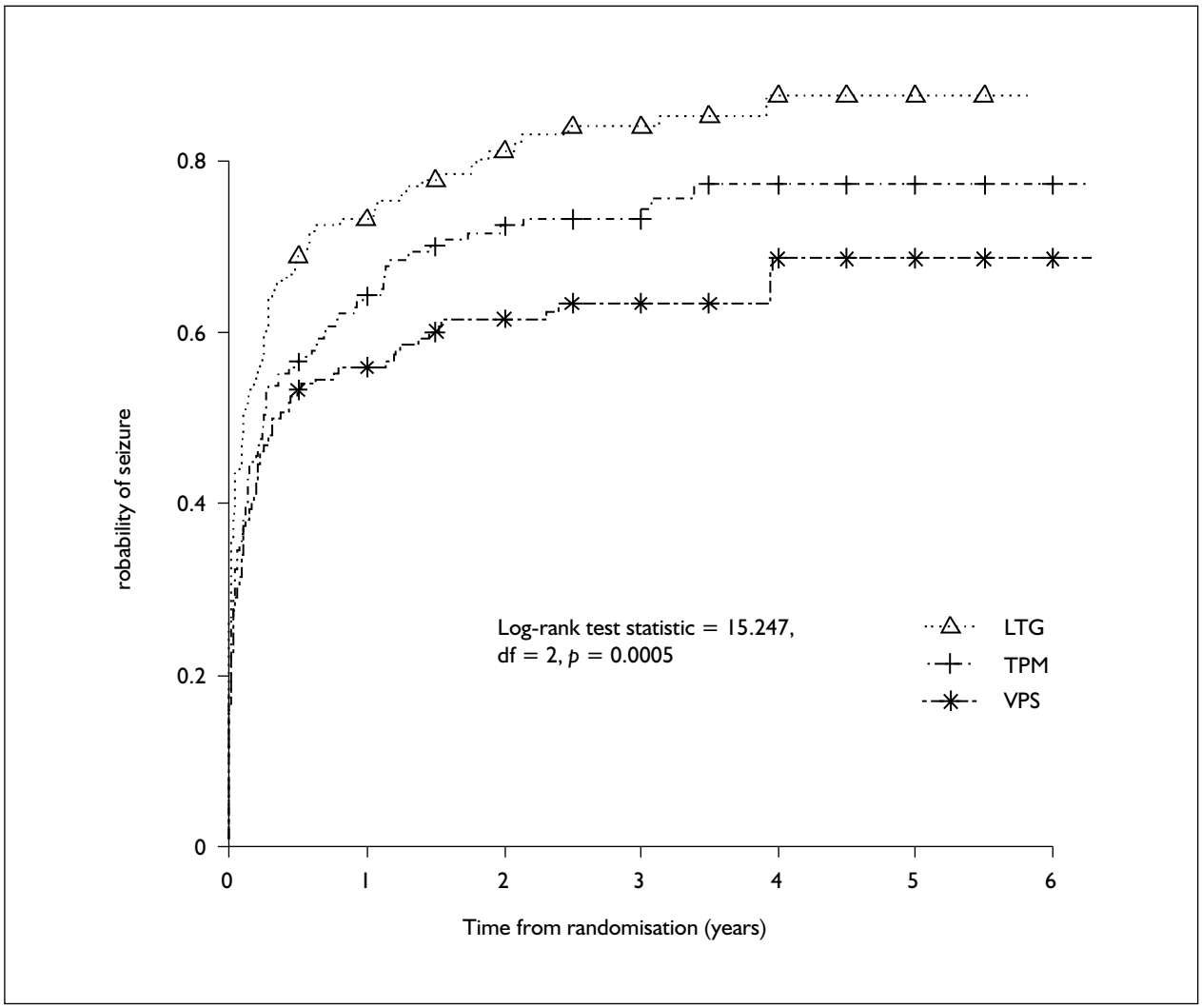


Drug (events/ total)		Year				
		1	2	3	4	5
VPS (137/226)	Number at risk	76	48	22	9	3
	% still on drug (95% CI)	55 (48 to 61)	58 (52 to 65)	61 (54 to 68)	69 (60 to 77)	69 (60 to 77)
LTG (162/227)	Number at risk	54	33	14	6	3
	Difference in % still on drug compared with CBZ (95% CI)	11 (2 to 20)	11 (2 to 20)	13 (4 to 22)	8 (–3 to 20)	8 (–3 to 20)
TPM (142/224)	Number at risk	66	35	19	12	6
	Difference in % still on drug compared with CBZ (95% CI)	2 (–7 to 11)	5 (–4 to 15)	4 (–6 to 13)	–3 (–14 to 8)	–3 (–14 to 8)

HR[a] (95% CI)	Baseline drug		
	VPS	LTG	TPM
VPS	–	*0.75 (0.60 to 0.94)*	0.97 (0.77 to 1.22)
LTG	*1.34 (1.07 to 1.68)*	–	*1.30 (1.04 to 1.62)*
TPM	1.03 (0.82 to 1.30)	*0.77 (0.62 to 0.96)*	–

[a] HR > 1 indicates that first seizure occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 51 *Time to first seizure (Arm B) as PP analysis*



Drug	Events	Total
LTG	118	141
TPM	108	145
VPS	98	152
Total	324	438

HR[a] (95% CI)	Baseline drug		
	VPS	LTG	TPM
VPS	–	*0.59 (0.45 to 0.77)*	0.80 (0.61 to 1.05)
LTG	*1.69 (1.29 to 2.22)*	–	*1.35 (1.04 to 1.76)*
TPM	1.25 (0.95 to 1.64)	*0.74 (0.57 to 0.96)*	–

[a] HR > 1 indicates that first seizure occurs more rapidly on drug compared with baseline. Italic indicates statistical significance.

FIGURE 52 *Time to first seizure (Arm B, generalised syndromes only) for entire recruitment period*

TABLE 55 *HR estimates and 95% CIs from Cox regression models adjusted for drug, epilepsy syndrome and drug–syndrome interaction terms*

Outcome (*p*-value from test for interaction)	Drug comparison	Unclassified	Partial/other	IGE
Time to treatment failure ($p = 0.12$)	LTG:VPS	0.88 (0.49 to 1.58)	0.70 (0.28 to1.73)	*1.56 (1.08 to 2.25)*
	TPM:VPS	1.33 (0.77 to 2.29)	0.51 (0.16 to 1.60)	*1.90 (1.33 to 2.71)*
Time to 12-month remission ($p = 0.04$)	LTG:VPS	0.91 (0.60 to 1.40)	0.81 (0.38 to 1.73)	*0.69 (0.53 to 0.89)*
	TPM:VPS	0.81 (0.52 to 1.24)	*2.53 (1.18 to 5.42)*	0.83 (0.64 to 1.07)
Time to 24-month remission ($p = 0.007$)	LTG:VPS	0.79 (0.47 to 1.32)	1.36 (0.42 to 4.46)	*0.60 (0.43 to 0.83)*
	TPM:VPS	*0.58 (0.34 to 1.00)*	*4.71 (1.58 to 14.06)*	*0.69 (0.50 to 0.94)*
Time to first seizure ($p = 0.001$)	LTG:VPS	1.05 (0.65 to 1.69)	1.37 (0.71 to 2.66)	*1.73 (1.32 to 2.26)*
	TPM:VPS	1.33 (0.84 to 2.10)	*0.30 (0.12 to 0.77)*	1.26 (0.96 to 1.65)

IGE, idiopathic generalised epilepsy.
Italic indicates statistical significance.

Adverse events

Adverse events were documented by clinicians as in Arm A. *Table 56* summarises ITT rates of adverse events considered clinically important. An ITT approach summarises adverse events associated with the randomised policy, but as patients may have had their treatment changed during follow-up, an ITT approach does not clearly present adverse events attributable to specific drugs. In *Table 57*, therefore, we present a PP summary of adverse events. *Table 58* summarises adverse events that were present close to the point of treatment failure with each drug. In each table, individual symptoms have been sorted by order of frequency of reporting.

It is notable that between 36% (VPS) and 45% (TPM) of patients reported adverse events at some point in the study (ITT). Estimates for the PP population were between 30% for VPS and 41% for TPM.

For the individual symptoms reported, tiredness and fatigue, psychiatric symptoms (most frequently for TPM) and weight gain (most frequently associated with VPS) were the most common symptoms. Rash was a non-central nervous system symptom, most particularly with LTG. These adverse event profiles were consistent across ITT and PP summaries.

The adverse events associated with treatment failure were most commonly psychiatric and cognitive symptoms and tiredness and fatigue, all of which were much more common with TPM. For LTG rash was the most common symptom associated with treatment failure, whereas for VPS weight gain was the most common such symptom. It should be noted that in the study neither patients nor clinicians were blind to drug treatment so that this may have influenced the symptoms reported to the clinicians and their assessment of the clinical importance.

QoL outcomes

A total of 428 adults sent baseline QoL questionnaires were randomised into Arm B. Response rates in this arm of the trial are presented in *Table 59*. No statistically significant differences in response by treatment group were observed.

As for Arm A, this analysis reports findings for the core QoL outcomes only. *Tables 60–67* present scores (with 95% CIs) for the core QoL measures at 2 years by treatment group adjusted for baseline values. As for Arm A, in each table columns

TABLE 56 *Arm B – frequency of clinically important adverse events (sorted by total frequency)*[a]

	LTG	TPM	VPS	Total
Number randomised	239	239	238	716
Total number (%) of patients with at least one adverse event	88 (37%)	107 (45%)	85 (36%)	280 (39%)
Total number of patients with each adverse event (sum of values in bold)	150	223	150	523
Total number of adverse events (sum of values not in bold)	187	283	184	654
Tiredness/drowsiness/fatigue/lethargy	**15** 22	**25** 35	**18** 20	**58** 77
Other psychiatric	**7** 9	**19** 27	**8** 11	**34** 47
Weight gain	**8** 13	**7** 10	**17** 24	**32** 47
Behaviour/personality change/aggression	**6** 8	**20** 34	**4** 4	**30** 46
Worsening of seizures	**10** 14	**13** 14	**7** 10	**30** 38
Accidental injury	**11** 14	**5** 7	**4** 4	**20** 25
Other neurological	**4** 4	**7** 7	**10** 13	**21** 24
Headache	**6** 9	**7** 7	**5** 7	**18** 23
Memory problems	**2** 2	**12** 15	**3** 4	**17** 21
Weight loss	**3** 3	**14** 17	**0** 0	**17** 20
Allergic rash	**13** 14	**1** 1	**2** 3	**16** 18
Tremor	**4** 7	**1** 1	**8** 9	**13** 17
Depression	**1** 1	**9** 11	**3** 4	**13** 16
Confusion/difficulty thinking/disoriented	**3** 3	**7** 9	**3** 3	**13** 15
Dizziness/vertigo	**3** 3	**6** 8	**1** 3	**10** 14
Anxiety/agitation/nervousness	**7** 9	**2** 2	**1** 1	**10** 12
Nausea	**4** 5	**2** 3	**4** 4	**10** 12
Other renal tract/genital	**4** 4	**4** 5	**3** 3	**11** 12
Pins and needles/dysaesthesia	**0** 0	**8** 10	**2** 2	**10** 12
Ataxia	**4** 5	**3** 3	**2** 3	**9** 11
Other skin and appendages	**1** 1	**5** 5	**5** 5	**11** 11
Mouth/gum problem	**1** 1	**2** 3	**3** 6	**6** 10
Sleep disturbance	**3** 5	**4** 4	**1** 1	**8** 10
Other[b]	**30** 31	**40** 45	**36** 40	**106** 116

[a] Values in bold represent the number of patients who have reported a specific side-effect. Other values represent the number of reported occurrences of a specific side-effect.

[b] Sorted by descending total frequency: abdominal pain, dyspepsia; allopecia; other general; other visual disturbance; word finding difficulty; vomiting; aches and pains; other gastrointestinal; other musculoskeletal; other respiratory/pulmonary; diarrhoea; psychosis; anorexia; bruising; constipation; diplopia; renal/bladder stones; flu-like symptoms; hallucinations; Infection; vaginal bleeding; arthritis; asthma; chest infection; childbirth; faints; hypertension; ischaemic heart disease/myocardial infarct; other cardiac/vascular; other haematological; psoriasis; short of breath; status epilepticus; UTI; urinary retention.

represent the baseline comparator: for example, in the VPS column, scores are for the other groups **compared with** VPS; values for continuous measures are the coefficients from a multiple regression representing the difference between treatments, with 95% CIs; and values for ordinal measures are the exponentiated coefficients from a proportional odds model, with 95% CIs, such that the values represent the odds of increasing severity of outcome.

For Arm B, there were no statistically significant differences in QoL between treatment groups, and few trends in the data with regard to direction of treatment effects. However, there was a suggestion of an increased likelihood of anxiety for LTG compared with TPM and VPS (*Tables 60* and *65*) (although the size of the increase was small and the 95% CIs wide), and there was a suggestion of an increased likelihood of depression for VPS compared with LTG or TPM (*Tables 61* and *66*) (although again the differences were small and the 95% CIs wide). There were no important differences or trends for scores on the AEP, the Neurotoxicity Scale, the EQ-5D or for GQoL.

As for Arm A, the results for this analysis need to be interpreted with caution, given the differences identified in baseline QoL profiles for responders and non-responders (Appendix 7).

TABLE 57 *Arm B – frequency of clinically important adverse events (sorted by total frequency) as PP (adverse events experienced up to withdrawal of drug or last follow-up for PP population)*[a]

	LTG	TPM	VPS	Total
Number randomised	227	226	228	681
Total number (%) of patients with at least one adverse event	73 (32%)	92 (41%)	69 (30%)	234 (34%)
Total number of adverse events experienced once or more by a patient (sum of values in bold)	105	160	105	370
Total number of adverse events (sum of values not in bold)	122	201	129	452
Tiredness/drowsiness/fatigue/lethargy	**9** 10	**20** 27	**12** 14	**41** 51
Behaviour/personality change/ aggression	**4** 5	**18** 28	**4** 4	**26** 37
Other psychiatric	**4** 4	**15** 21	**7** 7	**26** 32
Weight gain	**5** 6	**2** 3	**16** 23	**23** 32
Worsening of seizures	**6** 8	**9** 10	**3** 3	**18** 21
Headache	**4** 6	**4** 4	**4** 6	**12** 16
Accidental injury	**7** 9	**3** 4	**2** 2	**12** 15
Memory problems	**2** 2	**10** 13	**0** 0	**12** 15
Weight loss	**0** 0	**12** 15	**0** 0	**12** 15
Allergic rash	**12** 13	**1** 1	**0** 0	**13** 14
Other neurological	**3** 3	**4** 4	**5** 7	**12** 14
Confusion/difficulty thinking/disoriented	**2** 2	**7** 9	**2** 2	**11** 13
Depression	**1** 1	**6** 7	**3** 4	**10** 12
Anxiety/agitation/nervousness	**6** 8	**2** 2	**1** 1	**9** 11
Dizziness/vertigo	**2** 2	**3** 5	**1** 3	**6** 10
Other[b]	**38** 43	**44** 48	**45** 53	**127** 144

[a] Values in bold represent the number of patients who have reported a specific side-effect. Other values represent the number of reported occurrences of a specific side-effect.

[b] Sorted by descending total frequency: mouth/gum problem; nausea; sleep disturbance; tremor; abdominal pain, dyspepsia; ataxia; other renal tract/genital; other skin and appendages; alopecia; other visual disturbance; pins and needles/dysaesthesia; word finding difficulty; vomiting; diarrhoea; other general; other musculoskeletal; other respiratory/pulmonary; anorexia; bruising; constipation; renal/bladder stones; hallucinations; infection; other gastrointestinal; vaginal bleeding; aches and pains; asthma; diplopia; flu-like symptoms; other haematological; psoriasis; psychosis; short of breath; urinary retention.

QoL outcomes by achievement of a 12-month remission or withdrawal of original AED

As in Arm A, there were differences for QoL between patients experiencing a positive (i.e. remission of seizures) clinical outcome and those who did not, and between patients experiencing a negative (i.e. treatment failure of the original randomised drug) clinical outcome and those who did not (*Tables 68* and *69*); although in this arm, for a number of comparisons, the differences did not reach the level of statistical significance and the 95% CIs were fairly wide. Nonetheless, the direction of effects was as for Arm A, indicating better QoL for those who achieved remission or had not been withdrawn from the randomised drug.

Health economic outcomes

Cost per QALY analysis

As with Arm A, tests of differences in baseline EQ-5D values between the groups were performed, with no statistically significant differences being found.

VPS, LTG, TPM

This analysis is based on 165 adult patients who provided complete EQ-5D responses. The numbers of patients in each drug group are VPS = 59, LTG = 53, and TPM = 53.

Table 70 shows the breakdown of hospitalisation resource use and 'other' resource use among patients.

Table 71 shows the contribution of AED costs, hospitalisation costs and 'other' costs to the average cost per patient.

Table 72 shows the point estimates of the ICERs for LTG and TPM. As with Arm A, these ICERs are estimated using the lowest costs of the relevant AEDs (VPS_{low} and LTG_{low}).

TABLE 58 *Most recent adverse event (sorted by total frequency) reported before treatment failure for UAE or UAE + ISC (Arm B) based on PP population*[a]

	LTG	TPM	VPS	Total
Number randomised	227	226	228	681
Number of treatment failures for UAE	25 (11%)	57 (25%)	35 (15%)	117 (17%)
Number of treatment failures for UAE and ISC	7 (3%)	18 (8%)	11 (5%)	36 (5%)
Clinically important				
Behaviour/personality change/aggression	3	10	1	14
Other psychiatric	1	10	3	14
Tiredness/drowsiness/fatigue/lethargy	1	10	3	14
Allergic rash	9	1	0	10
Memory problems	0	9	0	9
Weight gain	0	0	8	8
Confusion/difficulty thinking/disoriented	0	6	1	7
Weight loss	0	6	0	6
Anxiety/agitation/nervousness	3	1	1	5
Ataxia	1	2	2	5
Other visual disturbance	3	1	0	4
Abdominal pain, dyspepsia	1	0	3	4
Depression	0	4	0	4
Nausea	3	1	0	4
Pins and needles/dysaesthesia	0	4	0	4
Other[b]	5	16	15	36
Not known	2	4	4	10
Not clinically important				
Failure for UAE	5	15	11	31
Failure for UAE + ISC	2	5	3	10

[a] Tabulated values represent the number of patients who have reported a specific side-effect.
[b] Sorted by descending total frequency: diarrhoea; headache; other neurological; sleep disturbance; tremor; vomiting; word finding difficulty; alopecia; accidental injury; dizziness/vertigo; worsening of seizures; anorexia; hallucinations; other haematological; other renal tract/genital; other skin and appendages; short of breath; vaginal bleeding.

TABLE 59 *QoL study response rates in Arm B across the whole time period*[a]

	VPS (%)	LTG (%)	TPM (%)	*p*-Value
Sent a baseline questionnaire	135	135	127	
Returned a baseline questionnaire	111 (82)	108 (80)	97 (76)	0.497
Returned a 2-year questionnaire	74 (55)	68 (50)	70 (55)	0.685
Returned a baseline and a 2-year questionnaire	73 (54)	68 (50)	68 (54)	0.806

[a] In this table, the analysis excludes 1 individual who was non-English speaking and 30 whose QoL assessment was pending/not due.

TABLE 60 *Two-year anxiety scores*

	LTG	TPM	VPS
LTG	–	0.97 (–0.28 to 2.22)	0.89 (–0.34 to 2.12)
TPM	–0.97 (–2.22 to 0.28)	–	–0.08 (–1.31 to 1.15)
VPS	–0.89 (–2.12 to 0.34)	0.08 (–1.15 to 1.30)	–

TABLE 61 *Two-year depression scores*

	LTG	TPM	VPS
LTG	–	–0.08 (–1.03 to 0.87)	–0.48 (–1.41 to 0.45)
TPM	0.08 (–0.87 to 1.03)	–	–0.40 (–1.34 to 0.54)
VPS	0.48 (–0.45 to 1.41)	0.40 (–0.54 to 1.34)	–

TABLE 62 *Two-year AEP scores*

	LTG	TPM	VPS
LTG	–	0.75 (–2.56 to 4.06)	0.73 (-2.52 to 3.98)
TPM	–0.75 (–4.06 to 2.56)	–	–0.08 (-3.29 to 3.26)
VPS	–0.73 (–3.98 to 2.52)	0.02 (–3.26 to 3.29)	–

TABLE 63 *Two-year neurotoxicity scale scores*

	LTG	TPM	VPS
LTG	–	–0.93 (–5.14 to 3.29)	–1.29 (–5.34 to 2.75)
TPM	0.93 (–3.29 to 5.14)	-	–0.37 (–4.48 to 3.75)
VPS	1.29 (–2.75 to 5.34)	0.37 (–3.75 to 4.48)	–

TABLE 64 *Two-year EQ-5D scores*

	LTG	TPM	VPS
LTG	–	–0.02 (–0.08 to 0.04)	0.02 (–0.04 to 0.08)
TPM	0.02 (–0.04 to 0.08)	–	0.04 (–0.02 to 0.10)
VPS	–0.02 (–0.08 to 0.04)	–0.04 (–0.10 to 0.02)	–

TABLE 65 *Two-year anxiety scores – ordinal*

	LTG	TPM	VPS
LTG	–	1.62 (0.71 to 3.72)	1.40 (0.64 to 3.10)
TPM	0.62 (0.27 to 1.42)	–	0.87 (0.37 to 2.00)
VPS	0.71 (0.32 to 1.58)	1.16 (0.50 to 2.68)	–

TABLE 66 *Two-year depression scores – ordinal*

	LTG	TPM	VPS
LTG	–	1.02 (0.38 to 2.78)	0.82 (0.33 to 2.07)
TPM	0.98 (0.36 to 2.67)	–	0.81 (0.31 to 2.09)
VPS	1.22 (0.48 to 3.08)	1.24 (0.48 to 3.23)	

TABLE 67 *Two-year GQoL scores*

	LTG	TPM	VPS
LTG	–	1.24 (0.66 to 2.34)	1.17 (0.64 to 2.16)
TPM	0.81 (0.43 to 1.53)	–	0.95 (0.51 to 1.77)
VPS	0.85 (0.46 to 1.57)	1.06 (0.57 to 1.97)	–

TABLE 68 *Arm B – QoL outcomes by whether a 12-month remission was achieved*

QoL measure	Effect	Estimate (95% CI)
Anxiety	Difference	–1.76 (–2.24 to –1.28)
Depression	Difference	–1.39 (–1.79 to –0.99)
ABNAS	Difference	–6.12 (–7.86 to –4.39)
AEP	Difference	–3.46 (–4.65 to –2.27)
EQ-5D	Difference	0.07 (0.04 to 0.09)
Anxiety	Odds ratio	0.45 (0.34 to 0.60)
Depression	Odds ratio	0.43 (0.31 to 0.59)
GQoL	Odds ratio	0.44 (0.34 to 0.56)

TABLE 69 *Arm B: QoL outcomes by treatment failure of randomised drug by 2-year follow-up*

QoL measure	Effect	Estimate (95% CI)
Anxiety	Difference	1.28 (0.81 to 1.77)
Depression	Difference	0.99 (0.59 to 1.39)
ABNAS	Difference	5.32 (3.59 to 7.04)
AEP	Difference	3.63 (2.48 to 4.78)
EQ-5D	Difference	–0.04 (–0.07 to –0.01)
Anxiety	Odds ratio	1.96 (1.48 to 2.59)
Depression	Odds ratio	1.99 (1.44 to 2.73)
GQoL	Odds ratio	1.54 (1.21 to 1.97)

TABLE 70 *Breakdown of resource use*

Item of resource use	Number of patients reporting contact			Average number of contacts among patients reporting contact (95% CI)		
	VPS	TPM	LTG	VPS	TPM	LTG
Hospitalisations[a]						
ICU	0	0	0	0	0	0
Psychiatric ward	0	0	0	0	0	0
Medical ward	2	2	1	5 (–45.8 to 55.8)	1	1
Surgical ward	2	0	2	30.5 (–293.5 to 354.5)	0	10 (–104.4 to 124.4)
A&E	0	1	2	0	1	1.5 (–4.9 to 7.9)
Other	0	1	1	0	3	1
Other[b]						
Nurse at GP surgery	16	7	12	11.1 (2.1 to 20.2)	6.3 (3.8 to 8.8)	11.1 (–2.6 to 24.7)
GP at surgery	36	27	24	9.4 (4.8 to 14.1)	7.3 (5.1 to 9.4)	15.2 (–3.5 to 33.9)
Nurse at home	13	1	2	5.6 (1.7 to 9.5)	6	3.0 (1.1 to 5.0)
GP at home	4	3	2	11.0 (2.4 to 19.7)	3.7 (1.3 to 6.0)	2.0 (0.1 to 4.0)
Ambulance	7	8	5	5.1 (0.6 to 9.7)	3.5 (2.1 to 4.9)	5.6 (1.6 to 9.6)
Blood test	20	24	11	6.3 (3.3 to 9.3)	3.9 (2.8 to 4.9)	5.1 (2.1 to 8.1)
Urine test	9	9	4	4.1 (2.4 to 5.8)	3.3 (2.0 to 4.6)	1.3 (0.8 to 1.7)
Ultrasound	2	3	0	5.0 (3.1 to 7.0)	3.7 (0.8 to 6.5)	0
X-ray	0	7	7	0	3.4 (1.4 to 5.4)	2.7 (1.2 to 4.2)
CT scan	9	12	7	1.6 (0.8 to 2.3)	1.4 (0.6 to 2.2)	1.7 (0.8 to 2.6)
MRI scan	5	8	14	2.0 (0.8 to 3.2)	2.3 (0.9 to 3.6)	2.4 (1.4 to 3.4)
EEG	24	18	20	1.1 (0.9 to 1.4)	1.1 (0.9 to 1.3)	1.5 (1.0 to 1.9)
Health visitor	1	1	0	4	13	0
Social worker	4	0	1	6.0 (0.1 to 11.9)	0	3
Disablement resettlement officer	1	0	0	4	0	0
Psychologist	2	3	0	2.0 (0.1 to 4.0)	2.7 (2.0 to 3.3)	0
Counsellor	2	1	4	8.0 (4.1 to 11.9)	3	2.3 (1.3 to 3.2)
Educational/vocational officer	1	2	1	1	5.0 (–2.8 to 12.8)	4

[a] Resource use associated with the management of adverse events requiring hospitalisation.
[b] Other healthcare and social services resource use.

TABLE 71 *The contribution of AED costs, hospitalisation costs and 'other' costs to the average cost per patient*

AED	Average cost per patient (£) (95% CI)	Breakdown of average cost per patient (£) (95% CI)		
		AEDs	Hospitalisation[a]	Other[b]
VPS	1390 (369 to 2411)	386 (247 to 526)	436 (–351 to 1221)	568 (220 to 916)
TPM	1568 (1303 to 1832)	1038 (911 to 1164)	91 (–12 to 194)	439 (262 to 616)
LTG	1906 (1405 to 2408)	1185 (1058 to 1311)	159 (–133 to 451)	562 (278 to 847)

[a] Costs associated with the management of adverse events requiring hospitalisation.
[b] Other healthcare and social services costs.

TABLE 72 *ICERs for the new AEDs*

AED	Cost (£)	QALYs	Incremental cost (£)	Incremental QALYs	ICER (£/QALY)
VPS	1390 (369 to 2411)	1.648 (1.51 to 1.79)	–	–	–
TPM	1568 (1303 to 1832)	1.809 (1.74 to 1.88)	178	0.161	1106
LTG	1906 (1405 to 2408)	1.701 (1.61 to 1.79)	338	–0.108	Dominated

LTG has a positive incremental cost and a negative incremental QALY gain and is therefore dominated by TPM. The same pattern of results is found when using different combinations of high and low costs for VPS and LTG. The lowest value of the ICER for TPM is when VPS_{high} and LTG_{high} are used and is equal to £692. The highest value is £1106 (reported in *Table 72*) when VPS_{low} and LTG_{low} are used.

The results of the sensitivity analysis on the assumptions made in the AUC approach to estimating QALYs did not impact on the relative ICERs (and therefore the pattern of results). The baseline estimate of the ICER for TPM relative to VPS (£1106) ranged from £1035 to £1633 depending on the assumptions made.

TABLE 73 *Probabilities that the new AEDs are cost-effective relative to VPS across a range of ceiling ratios (λ)*

Ceiling ratio, λ (£)	Probability new AED is cost-effective	
	LTG	TPM
10,000	0.53	0.91
30,000	0.68	0.97
50,000	0.70	0.98

Cost-effectiveness acceptability curves. Bootstrapping the baseline point estimate for the ICER for TPM relative to VPS results in 67% of the replications being located in the NE quadrant of the cost-effectiveness plane (more costly, more effective), with a further 2% being located in the NW quadrant (more costly, less effective). Interestingly, the remaining 31% of the replications are located in the SE quadrant, where the new treatment is both less costly and more effective and therefore dominates VPS.

Figure 53 shows the CEAC for TPM relative to VPS and *Figure 54* shows the corresponding CEAC for LTG relative to VPS. The probabilities that TPM and LTG are cost-effective at ceiling ratios of £10,000, £30,000 and £50,000 per QALY are presented in *Table 73*.

Cost per seizure avoided analysis, adults and children combined

VPS, LTG, TPM

This analysis is based on 299 patients, with the numbers of patients in each drug group being VPS = 101, LTG = 102 and TPM = 96.

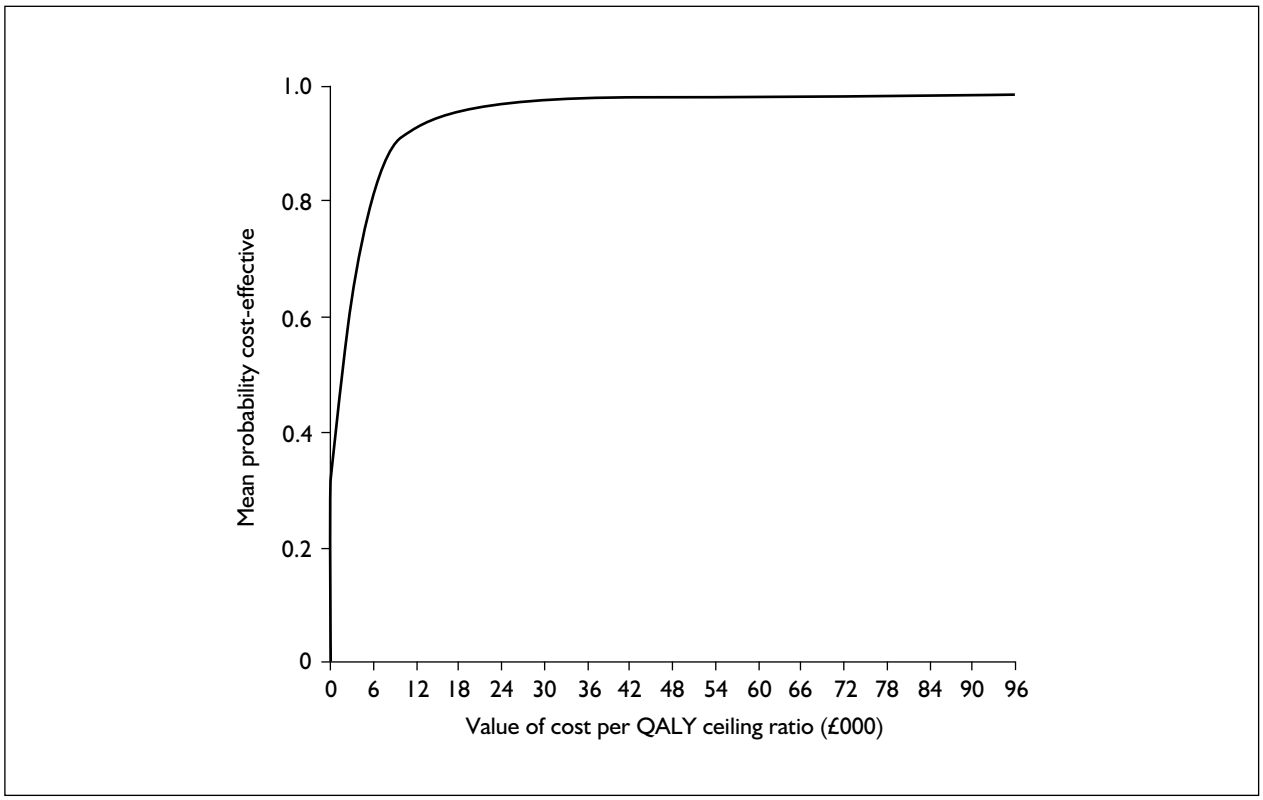


FIGURE 53 *CEAC for TPM relative to VPS*

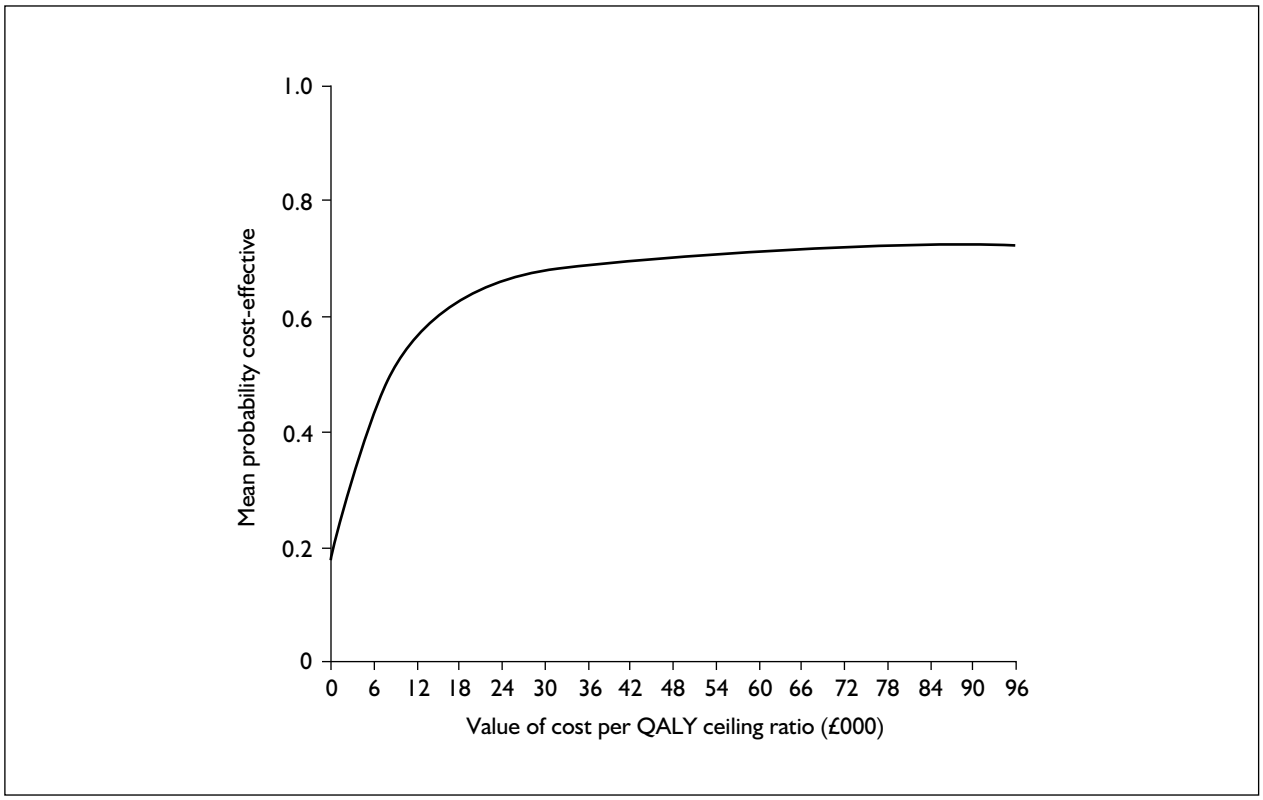


FIGURE 54 *CEAC for LTG relative to VPS*

TABLE 74 *Breakdown of resource use*

Item of resource use	Number of patients reporting contact			Average number of contacts among patients reporting contact (95% CI)		
	VPS	TPM	LTG	VPS	TPM	LTG
Hospitalisations[a]						
ICU	0	0	0	0	0	0
Psychiatric ward	0	1	0	0	100	0
Medical ward	3	2	2	5.3 (–4.7 to 15.4)	1	1.5 (–4.9 to 7.9)
Surgical ward	2	0	2	30.5 (–293.5 to 354.5)	0	10 (–104.4 to 124.4)
A&E	1	2	4	1	1.5 (–4.9 to 7.9)	1.25 (0.5 to 2.0)
Other	0	2	4	0	2.5 (–3.9 to 8.9)	1
Other[b]						
Nurse at GP surgery	20	9	14	10.8 (3.4 to 18.1)	5.6 (3.4 to 7.7)	12.3 (0.1 to 24.5)
GP at surgery	43	29	33	10.2 (6.1 to 14.2)	7.0 (4.9 to 9.0)	12.5 (–1.1 to 26.1)
Nurse at home	13	1	2	5.6 (1.7 to 9.5)	6	3.0 (1.1 to 5.0)
GP at home	5	3	2	9.0 (1.2 to 16.8)	3.7 (1.3 to 6.0)	2.0 (0.1 to 4.0)
Ambulance	10	11	8	4.4 (1.2 to 7.6)	2.8 (1.6 to 4.0)	6.3 (3.3 to 9.2)
Blood test	25	26	17	5.9 (3.5 to 8.3)	4.0 (3.0 to 5.0)	4.3 (2.3 to 6.3)
Urine test	11	10	8	3.6 (2.0 to 5.1)	3.4 (2.2 to 4.6)	1.9 (0.7 to 3.1)
Ultrasound	3	4	1	3.7 (0.8 to 6.5)	3.8 (1.7 to 5.8)	6
X-ray	2	7	8	2.0 (0.1 to 4.0)	3.4 (1.4 to 5.4)	3.4 (1.5 to 5.2)
CT scan	14	18	9	1.6 (0.9 to 2.3)	2.3 (0.6 to 4.0)	1.9 (1.0 to 2.8)
MRI scan	10	11	15	1.8 (1.0 to 2.6)	2.2 (1.1 to 3.2)	2.4 (1.5 to 3.3)
EEG	29	25	27	1.2 (0.9 to 1.6)	1.1 (0.9 to 1.2)	1.5 (1.1 to 1.9)
Health visitor	1	1	1	4	13	1
Social worker	4	0	1	6.0 (0.1 to 11.9)	0	3
Disablement resettlement officer	1	0	0	4	0	0
Psychologist	2	3	1	2.0 (0.1 to 4.0)	2.7 (2.0 to 3.3)	3
Counsellor	2	1	5	8.0 (4.1 to 11.9)	3	2.4 (1.6 to 3.2)
Educational/vocational officer	1	2	1	1	5.0 (–2.8 to 12.8)	4

[a] Resource use associated with the management of adverse events requiring hospitalisation.
[b] Other healthcare and social services resource use.

TABLE 75 *The contribution of AED costs, hospitalisation costs and 'other' costs to the average cost per patient*

AED	Average cost per patient (£) (95% CI)	Breakdown of average cost per patient (£) (95% CI)		
		AEDs	Hospitalisation[a]	Other[b]
VPS	1136 (529 to 1743)	325 (236 to 414)	273 (–188 to 733)	538 (321 to 755)
TPM	1568 (1378 to 1757)	1024 (927 to 1121)	58 (–1 to 117)	486 (350 to 623)
LTG	1761 (1466 to 2055)	1088 (990 to 1186)	93 (–60 to 245)	580 (394 to 766)

[a] Costs associated with the management of adverse events requiring hospitalisation.
[b] Other healthcare and social services costs.

Table 74 shows the breakdown of hospitalisation resource use and 'other' resource use among patients.

Table 75 shows the contribution of AED costs, hospitalisation costs and 'other' costs to the average cost per patient.

Table 76 shows the point estimates of the ICERs for LTG and TPM. As with Arm A, these ICERs are estimated using the lowest costs of the relevant AEDs (VPS_{low} and LTG_{low}).

TPM and LTG have positive incremental costs and negative incremental seizures avoided and are

TABLE 76 *ICERs for the new AEDs*

AED	Cost (£)	Seizures	Incremental cost (£)	Incremental seizures avoided	ICER (£/seizure avoided)
VPS	1136 (529 to 1743)	44.1 (17.4 to 70.9)	–	–	–
TPM	1568 (1378 to 1757)	75.1 (19.8 to 130.3)	432	–31.0	Dominated
LTG	1761 (1466 to 2055)	120.9 (59.2 to 182.6)	193	–45.8	Dominated

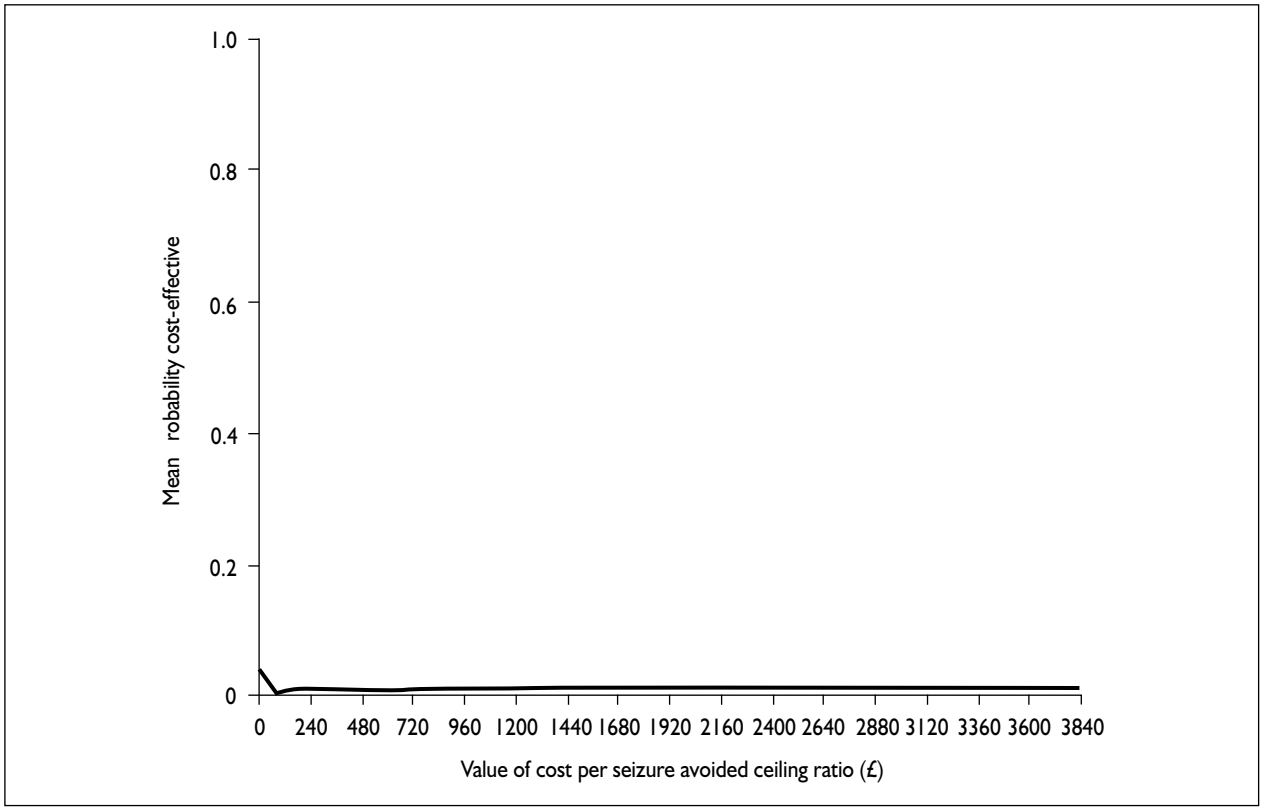


FIGURE 55 *CEAC for LTG relative to VPS*

therefore both dominated by VPS. The same pattern of results is found when using different combinations of high and low costs for VPS and LTG.

Cost-effectiveness acceptability curves. Bootstrapping the point estimate for the ICER for TPM relative to VPS results in 14% of the replications being located in the NE quadrant of the cost-effectiveness plane (more costly, more effective), 7% in the SW quadrant (less costly, less effective) and 2% in the SE quadrant (less costly, more effective). The majority of the replications (77%) are located in the NW quadrant, where the new treatment is more costly and less effective and therefore dominated by VPS.

Bootstrapping the point estimate for the ICER for LTG relative to VPS results in 1% of the replications being located in the NE quadrant of the cost-effectiveness plane (more costly, more effective) and 4% in the SW quadrant (less costly, less effective). The majority of the replications (95%) are located in the NW quadrant, where the new treatment is more costly and less effective and therefore dominated by VPS.

Figure 55 shows the CEAC for LTG relative to VPS and *Figure 56* shows the corresponding CEAC for TPM relative to VPS. The probabilities that LTG and TPM are cost-effective at ceiling ratios of £160, £400, £800 and £1600 per seizure avoided are presented in *Table 77*.

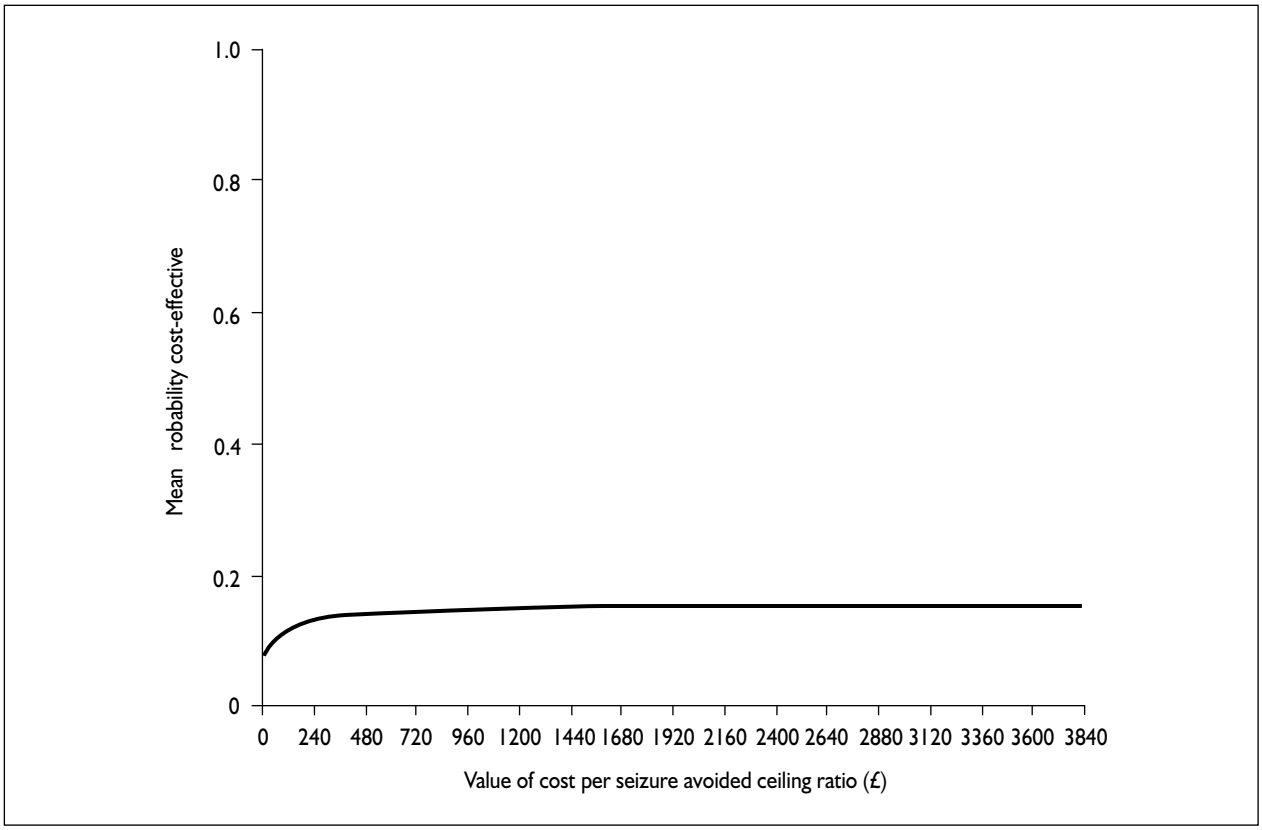


FIGURE 56 *CEAC for TPM relative to VPS*

TABLE 77 *Probabilities that the new AEDs are cost-effective relative to VPS across a range of ceiling ratios (λ)*

Ceiling ratio, λ (£)	**Probability new AED is cost-effective**	
	LTG	**TPM**
160	0.01	0.14
400	0.01	0.15
800	0.01	0.16
1600	0.01	0.16

Chapter 4
Discussion

SANAD was designed as a pragmatic trial to assess whether any of the newly licensed AEDs should become first-line treatment and thereby replace the existing first-line agents, CBZ and VPS. If there were clinical or QoL benefits from newer over established AEDs, we wished to assess the incremental costs associated with these benefits. Because epilepsy is a chronic disorder, we wished to assess treatments over relevant and long periods. Because of these aims, a number of decisions were made about the methodology used that are important to consider when assessing the results.

The most important single issue was that we wished the trial to have strong external validity so that results could be applied to everyday clinical practice. Because of this, entry criteria were as inclusive as possible and clinicians were encouraged to use their everyday clinical practice in the management of patients. We provided some guidelines for initial target drug dosing, but allowed clinicians to vary dosing on clinical grounds as they saw fit, throughout the course of the study, so as to ensure as far as possible that patients received optimal doses for seizure control on the one hand and avoided adverse effects on the other. We elected that the study be unmasked because this reflects more accurately clinical practice and because it greatly reduced the cost of the study, while increasing practicability. For a five-way comparison of drugs (in Arm A) the requirements for double dummy dosing and central provision of drug supplies for prolonged periods of follow-up would have presented enormous logistic problems and been prohibitively expensive. For a long study there would have been practical difficulties in maintaining masking for drugs that have differing interactions with important treatments such as oral contraceptives or warfarin. Similarly, management of women in the child-bearing years would have been greatly complicated.

All these decisions, particularly the lack of blinding, could be seen as compromising the internal validity of the study, but to compensate for these concerns we were able to randomise over 2400 patients and achieve a high level of follow-up (close to 8000 patient years), something that would have been impossible with a more explanatory shorter clinical trial.

The patients randomised were mainly newly diagnosed and treatment naïve, although some patients were entered who had been previously treated with AEDs not included in SANAD or inappropriate AEDs, or who had a previous history of epilepsy, had been treated, but who had now relapsed with recent seizures following withdrawal of AED treatment. As would be expected, a high proportion of patients went on to achieve 1- and 2-year remissions of epilepsy. Clinicians chose the most appropriate arm for patients by considering which of the two standard drugs would have been optimal for each subject. The case mixes in Arm A and Arm B were as expected. In Arm A (CBZ as standard drug), there was a majority of patients with partial onset seizures and cryptogenic or symptomatic localisation-related epilepsy, and patients were older. In Arm B, there was a high proportion of patients with idiopathic generalised epilepsy and also patients with unclassified epilepsy, indicating that clinicians viewed the drugs available in Arm B as having a broad spectrum of activity. In these respects, both the design of SANAD and the population recruited reflect everyday clinical practice. At randomisation, clinicians classified patients' seizure types and epilepsy syndrome according to ILAE definitions (including consideration of EEG and imaging data), but were also allowed to state that the precise seizure or syndrome classification was as yet unclassified if that was the case. This allowed the recruitment of patients with unclassified seizures and epilepsy. This approach enhances external validity in two ways. First, it results in a trial that informs treatment choices for patients whose seizure and epilepsy types clinicians find difficulty in classifying. Second, it avoids forcing clinicians to classify falsely a patient's syndrome where there is genuine uncertainty, thereby reducing misclassification errors, an issue that has confounded previous drug–drug comparisons, particularly those that have recruited patients with generalised onset seizures and epilepsy syndromes.[70]

The design and powering of the study were unusual, in that it was designed to allow some

assessment of equivalence between the drugs assessed. This was because of a concern that previous comparative drug studies in similar patients had shown differences in tolerability, but had failed to show differences in efficacy. It was therefore felt essential to address the possibility of equivalence, or at least non-inferiority, for efficacy. Thus, if a new AED showed superior tolerability to its standard comparator, we wished to have power and confidence to exclude clinically important differences in efficacy, before accepting the drug as being first choice according to clinical outcomes. This resulted in power calculations requiring 445 patients per treatment group. Although we were unable to recruit this number of patients, we were able to extend the length of the study, with an increase in the number of outcome events and corresponding protection of power. With the greater size and longer follow-up, it is evident that the failure of previous studies to demonstrate differences in efficacy was due to their being underpowered, and having much shorter follow-up, of patients. Real and clinically important differences in efficacy do indeed exist among AEDs.

We have presented two analyses of results: ITT and a PP analysis of clinical outcomes. In ITT analyses, clinical data after a treatment failure on the randomised drug are included. Thus these analyses are an analysis of a policy that comprised initial treatment with the randomised drug followed by, where necessary, switching to an alternative regime that most commonly was monotherapy with the standard drug from the respective study arms or, where the standard drug failed, LTG in each arm. In contrast, the PP analyses allowed censoring of observations at the time of a treatment failure outcome, so that only clinical information while on randomised drug is included. When considering the results for differences between drugs, the ITT analyses should be considered as most conservative, but when assessing possible equivalence, then PP analyses are more conservative and should be given greatest weight.[71]

SANAD was a national study, drawing in patients from 90 centres across the UK. For reasons of pragmatism, particularly the much greater costs of using other methods, we opted to collect QoL and some health economic information from patients using postal questionnaires. In doing so, we adopted an approach used successfully in our two previous randomised studies of treatment issues in epilepsy.[72,73] As in these previous studies, patient response rates at successive data collection waves were high, but inevitably, with this postal approach, there were some non-responders and hence some loss to follow-up and some patients who responded were nonetheless slow to respond. Our findings of differences between responders and non-responders for baseline QoL profile and trial clinical outcomes are in line with previous research showing that responders to surveys are likely to make favourable reports and to be more successful in their current status than non-responders.[74,75] The implications of this responder bias for interpretation of the QoL data and calculation of QALYs must therefore be borne in mind. It is possible that important QoL outcomes associated with the drugs were not detected, because patients for whom the QoL effects were most negative were those who opted not to respond at the various follow-ups. Likewise, the finding that some patients experienced an important clinical event before they returned their baseline questionnaire is important and represents a further potential source of contamination (although the numbers involved were small). Although not included in this report, a comparison of QoL outcomes of late versus early responders and the utility of imputing scores for non-responders from those of late responders will be considered in a separate analysis (and is currently the subject of an application for funding to the UK MRC).

The health economics analysis was conducted using two distinct ICERs, namely cost per QALY gained and cost per seizure avoided. Although number of seizures experienced by patients is clearly an important clinical outcome, it constitutes a narrow measure of 'benefit' in an economic evaluation in that it focuses on just one aspect of patient outcome. In contrast, the QALY is a much broader measure of benefit in that it purports to measure health-related QoL, which is affected by not only the various clinical outcomes but also other factors, such as the impact of drug side-effects on patients' health. In view of this, it is tempting to place greater weight on the cost per QALY results. However, it should be borne in mind that because patients who responded to the EQ-5D questionnaire were 'healthier' than their non-responding counterparts, the cost per QALY analysis is based on a potentially unrepresentative sample of trial patients. It is worth noting that 350/1014 (35%) of responders to the EQ-5D scale in the baseline QoL assessment had a score of 1 (representing full health), as did 409/991 (41%) of responders to the EQ-5D scale at 2-year follow-up. For a significant proportion of patients there was therefore no way that they could register any increments for QoL.

Arm A

The clinical results and their implications are clear. In Arm A, LTG has the lowest incidence of treatment failure and is statistically superior for this outcome to all drugs with the exception of OXC (when this comparison is restricted to patients randomised after 1 June 2001, the date after which OXC was added to the randomisation). The differences are clinically important, with 12% and 8% fewer patients experiencing treatment failure on LTG than CBZ at 1 and 2 years after randomisation, respectively. Competing risks analysis shows that LTG's superiority comes from its tolerability advantage over CBZ, as CBZ has fewest contributions to treatment failure from ISC and is the preferred drug for the primary efficacy outcome, time to 12-month remission and for the secondary efficacy outcomes of time to first seizure and 24-month remission. The difference between LTG and CBZ for time to 12-month remission is small compared with the difference in tolerability and not statistically significant. Indeed, the CIs around comparisons between CBZ and LTG for treatment failure due to ISC and time to 12-month remission are sufficiently small to infer non-inferiority of LTG for these outcomes (varying between 5 and 12% for both PP analyses). CBZ is superior to LTG for time to first seizure, but this efficacy outcome may be dependent on initial dosing and potentially indicates that initial LTG dosing in the trial was conservative, a conclusion that is supported by the way in which PP analysis of time to 12-month remission shows LTG catching up with and eventually overtaking CBZ. There is also a low rate of rash in patients randomised to LTG in this arm of the study compared with what might have been expected, a further potential consequence of conservative initial dosing.[76,77]

One further issue that may affect the LTG–CBZ comparison is the choice of prescribing CBZ as either a standard preparation or a modified release. We did not collect information systematically on this prescribing but a large majority of collaborating clinicians indicated that they routinely prescribe the modified rather than the standard release versions of the drug. We feel that prescribing of ordinary release CBZ was unlikely to have been frequent enough to have affected CBZ assessment adversely in the study.

The fact that SANAD recruited across a wide age range allowed us to assess whether the results from Arm A are as applicable to children and the elderly as they are to the greater number between the extremes of age. Although age itself does affect outcomes, with strong evidence that patients over the age of 65 years have a better seizure prognosis, there is no evidence of an interaction between age and treatment groups indicating that results are applicable through life. In this respect, there is some disagreement between SANAD and Rowan and colleagues,[78] who studied older patients with epilepsy and found that both LTG and GBP were preferred to CBZ in this age group.

Given the demonstration of superior tolerability of LTG over CBZ, with non-inferiority of longer-term efficacy outcomes, the clinical outcomes would support LTG as first-choice treatment for the majority of patients with partial epilepsy. Although the improved clinical outcomes are not reflected in improvements for individual domains of QoL, with the exception of depression, there is no evidence from QoL data that would detract from the clinical conclusion. In view of the striking clinical differences found, it may at first sight be puzzling that we have not demonstrated differences for QoL domains. We can be confident, however, that the measures used are sensitive given the fact that there are clear QoL benefits from achieving 12-month remission and clear QoL harms from experiencing a treatment failure. A number of factors may have contributed to the failure to detect more differences between treatment groups. These include the effects of responder bias (since non-responders were found to have poorer baseline QoL profiles and poorer clinical outcomes by the time of 2-year follow-up); the pragmatic nature of the trial, whereby clinicians were able to alter drug doses should their side-effects prove problematic and hence reduce or eliminate any adverse effects for QoL; and the spacing of the QoL assessments, which may have meant that decrements for QoL that were relatively short-term went undetected. Furthermore, it is important to bear in mind that the QoL analyses reported were ITT; by 2-year follow-up, these outcomes are therefore likely to reflect that clinicians and patients will, in response to a treatment failure, attempt to move towards an optimal treatment strategy, including modification of dose so as to maximise QoL.

The economic analysis lends support to LTG being preferred to CBZ in terms of both cost per seizure avoided and cost per QALY gained. With respect to the latter, there would appear to be a high probability that LTG is a cost-effective alternative to CBZ at what might reasonably be considered 'affordable' (to the NHS) values of the ceiling ratio (λ).

There are no reasons to prefer GBP or TPM to the standard drug CBZ. Both are associated with a higher risk of treatment failure, that just fails to reach significance, GBP because of poor efficacy and TPM because of poor tolerability and lesser efficacy than CBZ. The health economic assessment supports this view. The remaining uncertainty is around the CBZ–OXC comparison. For all clinical outcomes there is some similarity between the two, but the smaller numbers of patients available to the comparison do not allow us to conclude that they are equivalent. The economic analysis which includes OXC provides evidence to support OXC being preferred to CBZ. The point estimates of the incremental cost per seizure avoided are relatively low, ranging between £31 and £36. With respect to the cost per QALY analysis, the probability that OXC is a cost-effective alternative to CBZ is relatively high across the range of ceiling ratio values (λ). Indeed, data from this limited period of the study point towards OXC being the most cost-effective of the AEDs in Arm A.

A number of other studies have compared LTG with CBZ in similar populations, although over much shorter periods, and an individual patient data meta-analysis has been undertaken.[79] This shows that LTG is better tolerated and less likely to be associated with treatment failure, in agreement with SANAD. Time to first seizure also agreed with SANAD in indicating that time to first seizure tended to be longer for CBZ, but this is the first study that has allowed examination of the more clinically important time to 12-month remission efficacy outcome, where the difference between the two drugs is much smaller. Two studies have compared LTG and GBP and found little difference.[78,80] They were too short, however, to allow meaningful comparison of efficacy outcomes, so that the treatment failure outcomes reported in the studies were dominated by the drugs' similar and good tolerability.

TPM has been compared with standard AEDs in one trial in which clinicians chose either CBZ or VPS as the preferred standard AED.[35] The subgroup for whom CBZ was chosen as the standard drug had focal seizures and were randomly assigned to receive 600 mg carbamazepine daily, 100 mg topiramate daily or 200 mg TPM daily. For the analyses, data for the 100- and 200-mg TPM groups were pooled. No difference was found between TPM and CBZ for time to treatment withdrawal, time to first seizure or the proportion of patients seizure free for the last 6 months of follow-up. Although this trial found no difference for these outcomes, the CIs were wide and the results did not indicate equivalence; hence this trial falls short of providing data that informs a choice between CBZ and TPM.

Arm B

The study failed to achieve the desired recruitment to this arm, but we have been fortunate in the differences between drugs in this arm being larger than expected and there are sufficient events during prolonged follow-up to allow robust conclusions. One factor that could have reduced recruitment may have been a reluctance to randomise women in their child-bearing years into a study in which they could be allocated to treatment with VPS, a drug recognised as being associated with a relative high foetal malformation rate and a risk of neuro-developmental delay.[81] In keeping with this, 60% of patients randomised to this arm were males. Despite this, we have no reason to believe that the results cannot be applied to women.

The results identify VPS as first-choice treatment. About 60% of patients in this arm of the study were identified at randomisation as having an idiopathic generalised epilepsy, thereby providing unique RCT information on treatment in these syndromes; 25% of patients were unclassified at randomisation and could therefore have been patients with either partial or generalised seizures. It is of interest that the differences between drugs were greater in the subgroup of idiopathic generalised epilepsy patients than in the entire group of patients randomised to this arm and that interaction testing indicates that VPS might be the poorest drug for patients with partial and other epilepsy syndromes randomised to this arm of the study.

For time to treatment failure, VPS was the preferred drug with TPM being the poorest, this comparison being significant. The factors influencing this outcome were the superior tolerability of LTG compared with VPS (intermediate for failure for unacceptable adverse events) and TPM (worst). In contrast, VPS was least likely to be associated with treatment failure for ISC, followed by TPM, with LTG being poorest. There was a similar ordering of drugs when analysis was restricted to patients with idiopathic generalised epilepsy syndromes, but VPS became significantly better than both comparator drugs.

In keeping with this, VPS was the preferred drug for time to 12- and 24-month remission, being significantly superior to LTG for this outcome, with TPM intermediate. Although the differences were small in the ITT analysis, the superiority of VPS was enhanced in the PP analysis, indicating that the switching from LTG for ISC and from TPM for UAEs to VPS was largely responsible for obscuring VPS's superiority for this outcome in ITT analyses. A similar ordering of drugs for time-to first seizure was evident, with both VPS and TPM being significantly better than LTG.

It is of considerable interest that whereas LTG is the poorest option in Arm B, it is the preferred option in Arm A. Arm B was constructed as a trial of broad-spectrum AEDs so as to encourage the randomisation of patients with generalised and unclassified epilepsy. The claims for LTG to be regarded as a broad-spectrum AED are based on limited RCT data.[82–85] It is notable, however, that the best identified mechanism of its anti-seizure effect is that of an inhibitor of voltage-sensitive Na^+ channels, a mechanism that it shares with drugs with restricted spectrums of efficacy, such as CBZ and phenytoin. SANAD suggests LTG should not be regarded as a broad-spectrum AED, but should be reserved for treatment of partial seizures and localisation-related epilepsy syndromes.

The health economics analysis based on cost per seizure avoided supports the recommendation of the clinical results that VPS should remain the first-choice drug for idiopathic generalised or unclassified epilepsy. However, the cost per QALY analysis suggests that there is a high probability that TPM is a cost-effective alternative to VPS throughout the full range of values of the ceiling ratio (λ). This apparently conflicting result may be due to the QALY picking up effects on health-related QoL besides those attributable to seizures alone, or it may be due to some other phenomenon such as the unrepresentative patient sample on which the cost per QALY analysis is based.

In conclusion, SANAD would indicate that LTG should be avoided as monotherapy in idiopathic generalised epilepsy because of its poorer efficacy and that current options lie between VPS and TPM. The study was not designed or powered to examine pregnancy outcomes, something of concern, when VPS is used in women of child-bearing potential.[81] Unfortunately, evidence for the safety of TPM during pregnancy remains sparse, so that there will be persisting difficulty in optimising treatment for women with idiopathic generalised epilepsy during their child-bearing years. Improvements here will await further observational data on pregnancy outcomes from registries.

Chapter 5
Conclusions

The SANAD study has successfully demonstrated the feasibility of carrying out large, pragmatic epilepsy studies in the NHS in a way that would be difficult in many other healthcare systems. It has offered an opportunity to extend research to examine psychometric outcomes for the different drugs (results to be published elsewhere) and with DNA collection (funded by the Wellcome Trust) to form a unique pharmacogenetic resource for epilepsy. Deficiencies of current methodologies are highlighted and should be addressed by future empirical work. This includes the need to improve methods and strategies to maximise response to QoL questionnaires during a longer-term study, and the need for appropriate methods to collect utility data for children. The relative insensitivity of the EQ-5D to changes in QoL for people with epilepsy, a uniquely stigmatising and disabling condition, highlights the need for an alternative tool to estimate QALYs for people with epilepsy.

Since the design of the study, three further new AEDs have been licensed in the UK: levetiracetam, pregabalin and zonisamide. The same questions that applied to GBP, LTG, OXC and TPM now apply to these drugs, although for partial epilepsies they will now need to be compared with LTG and possibly OXC, rather than CBZ. SANAD has demonstrated that we have a robust methodology to answer the questions.

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Contribution of authors

AG Marson (Senior Lecturer) was involved in the trial design, day-to-day management, recruitment and analysis and in preparing the final report. RE Appleton (Consultant Paediatric Neurologist) was the paediatric neurology coordinator, sat on the trial management committee and was involved with the preparation of the final report. GA Baker (Professor of Neuropsychology) coordinated the collection of neuropsychological data, sat on the trial management committee and commented on the final report. DW Chadwick (Professor of Neurology) was the trial coordinator, sat on the trial management committee and was involved in the design, day-to-day management, recruitment and analysis and in preparing the final report. J Doughty (Research Associate) managed the mail-out exercise for collection of the QoL data; the coding, checking and data entry processes for the QoL information; and contributed to writing of the report on the QoL data. B Eaton (Trial Manager) was the trial manager and involved with the preparation of the final report. C Gamble (Lecturer in Medical Statistics) was the trial statistician for the quality of life outcome, sat on the trial management committee and was involved with the preparation of the final report. A Jacoby (Professor of Medical Sociology) was involved with the design of the trial, coordinated the collection of quality of life data and was involved with the preparation of the final report. P Shackley (Senior Lecturer in Health Economics) was involved with the health economic analysis, sat on the trial management committee and was involved in the preparation of the final report. DF Smith (Consultant Neurologist and Honorary Senior Lecturer) was involved with recruitment and the preparation of the final report. C Tudur-Smith (Senior Lecturer in Medical Statistics) was the trial statistician for clinical outcomes, prepared reports for the data monitoring committee, sat on the trial management committee and was involved in preparing the final report. A Vanoli (Senior Research Associate) was involved with the design and analysis of the health economic assessment, sat on the trial management committee and was involved with the preparation of the final report. PR Williamson (Professor of Medical Statistics) was the statistical team leader, sat on the trial management committee, commented on all versions of report and worked with trial statisticians in drafting statistical sections.

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Appendix 1

Adverse effects classification

Haematological

Anaemia
Neutropenia
Thrombocytopenia
Coagulation abnormality
Bruising
Malignancy
Other

Gastrointestinal

Anorexia
Nausea
Vomiting
Diarrhoea
Constipation
Peptic ulceration
Abdominal pain, dyspepsia
Malignancy
Weight gain
Weight loss
Mouth/gum problem
Other

Hepatobiliary

Abnormal liver function tests
Hepatitis
Obstructive jaundice
Gall bladder disease
Pancreatitis
Other

Renal tract/genital

Renal failure
Renal/bladder stones
Urinary retention
UTI
Vaginal bleeding
Impotence/libido problems
Malignancy
Other

Endocrine

Diabetes mellitus
Thyroid disease
Other

Respiratory/pulmonary

URTI, catarrh, sinusitis, rhinorrhoea
Short of breath
Infection
Fibrosis
Asthma
Malignancy
Other

Skin and appendages

Allergic rash
Eczema
Psoriasis
Allopecia
Other

Cardiac/vascular

Ischaemic heart disease/myocardial infarct
Conduction abnormality
Tachycardia
Hypertension
Venous thrombosis
Faints
Other

Neurological

Stroke–infarction
Haemorrhage
Headache
Ataxia
Diplopia
Other visual disturbance
Tiredness/drowsiness/fatigue/lethargy
Dizziness/vertigo
Hearing problem/tinnitus
Word finding difficulty
Confusion/difficulty thinking/disoriented
Memory problems
Sleep disturbance
Pins and needles/dysaesthesia
Tremor
Worsening of seizures
Status epilepticus
Other

Psychiatric

Depression
Anxiety/agitation/nervousness
Behaviour/personality change, aggression
Psychosis
Hallucinations
Other

Musculoskeletal

Aches and pains
Myalgia
Arthritis
Other

General

Flu-like symptoms
Accidental injury
Childbirth
Other

Appendix 2

QoL analysis. Comparison of baseline response rates and time to respond by contact letter type

The role of the covering letter in persuading recipients to participate in postal surveys has been highlighted by a number of survey researchers, and previous methodological studies have investigated the role of a range of aspects of the covering letter in promoting high levels of response. These have included style of letter, style of signature, nature of the appeal, specification of a deadline for return and provision of time cues indicating the length of time required to complete the questionnaire.[86] To investigate the effect of this last aspect, QoL participants were randomised to receive a covering letter with the QoL questionnaires that included or did not include an estimate of the length of time required to complete the questionnaire. In all, 1815 persons were randomised (this methodological exercise was not included as part of the pilot phase).

No differences between response rates or time taken to respond were identified between those who received the letter with time information and those who did not (*Table 78* and *Figure 57*). As the letter also stated which drug was considered to be

TABLE 78 *Response by QoL letter type – all participants*

	QoL letter did not include approx. time required to complete questionnaire	**QoL letter did include approx. time required to complete questionnaire**
No response at baseline	149 (16%)	135 (15%)
Responded at baseline	775 (84%)	756 (85%)
Totals	924	891
χ^2 *p*-value = 0.5680.		

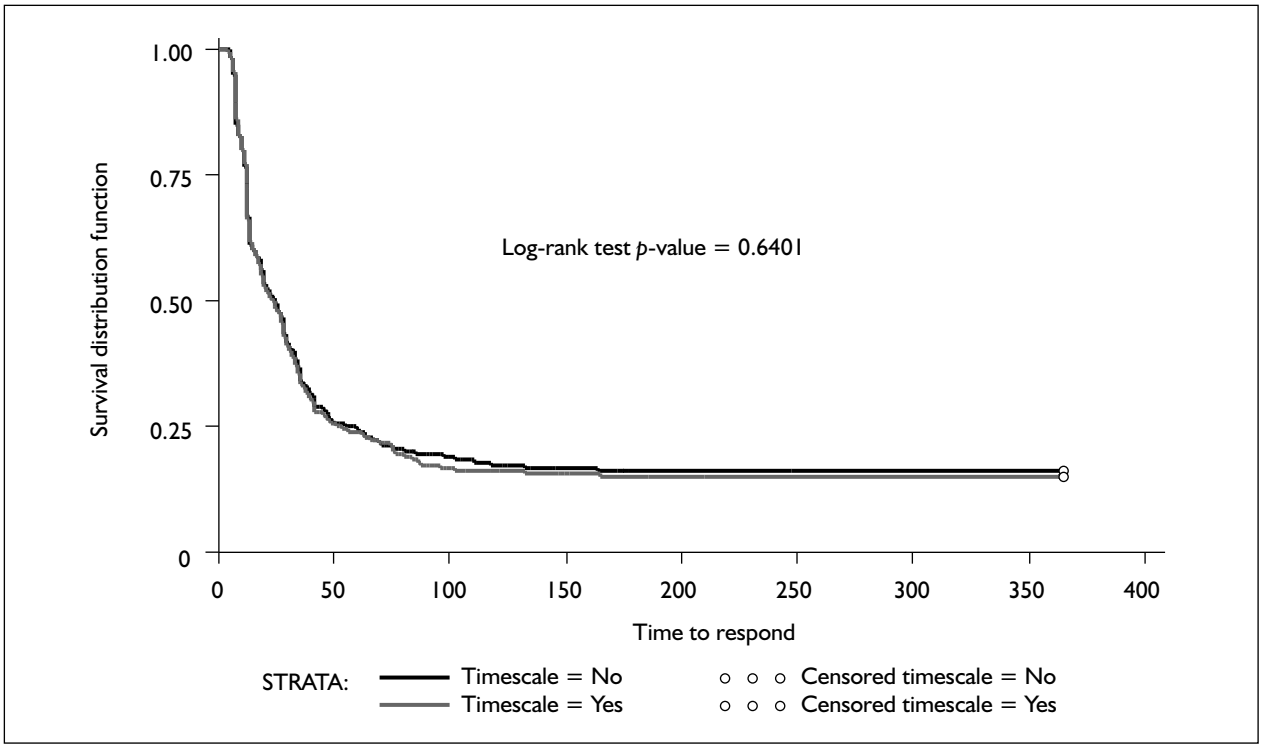

FIGURE 57 *Kaplan–Meier curve: time to respond by letter type – all participants*

TABLE 79 *Response at baseline by randomisation to new or standard AED – all participants*

	New AED	Standard AED
No response at baseline	228 (16%)	66 (14%)
Responded at baseline	1186 (84%)	401 (86%)
Totals	1414	467
χ^2 *p*-value = 0.3041.		

the standard, associations between response and whether participants had been randomised to receive the new or standard drug were considered, but no such association was identified (*Table 79*).

Covering letters sent to patients

Dear
SANAD: A multicentre study of standard and new antiepileptic drugs

You may remember that about a year ago you agreed to take part in the above study, which is concerned with whether the new drugs for epilepsy are effective and represent value for money. The results from the study will mean that in future, doctors will have better information to help their patients decide which course of treatment is best for them.

It is important that we take account of the views and experiences of all the patients taking part in the study, even when there has been a change in your situation (for example, when you have stopped taking medication or have stopped having seizures), if this very important question about treatment is to be answered satisfactorily.

As explained in the patient information leaflet you received when entering the study, now that you have taken part in the study for one year, we are writing to ask you to complete another questionnaire for us. This questionnaire will help us know how things have been for you and how you are feeling now. We would also like you to tell us about your use of health services and any costs you have incurred over the past three months because of any epileptic attacks and/or any associated injuries and/or any treatment side-effects you may have had.

We very much hope you will feel able to complete the enclosed questionnaire and return it in the pre-paid envelope – **no stamp is needed**. *We do not think it will take you more than 45 minutes to do so*.

Everything you tell us will be treated as **strictly confidential**. None of the information you give us will be passed on to anyone outside the study team. When the results of the study are presented, it will not be possible for individual patients to be identified in any way. You will see that we have also enclosed a pre-paid postcard which you can use in the future should you change your name or address, or now if we do not have your full details – again, no stamp is needed.

We will contact you again next year to see how things are for you then. We would like to take this opportunity to thank you once again for agreeing to help us with this important study.

Yours sincerely

Ann Jacoby
Professor of Medical Sociology

Dear
SANAD: A multicentre study of standard and new antiepileptic drugs

You may remember that about a year ago you agreed to take part in the above study, which is concerned with whether the new drugs for epilepsy are effective and represent value for money. The results from the study will mean that in future, doctors will have better information to help their patients decide which course of treatment is best for them.

It is important that we take account of the views and experiences of all the patients taking part in the study, even when there has been a change in your situation (for example, when you have stopped taking medication or have stopped having seizures), if this very important question about treatment is to be answered satisfactorily.

As explained in the patient information leaflet you received when entering the study, now that you have taken part in the study for one year, we are writing to ask you to complete another questionnaire for us. This questionnaire will help

us know how things have been for you and how you are feeling now. We would also like you to tell us about your use of health services and any costs you have incurred over the past three months because of any epileptic attacks and/or any associated injuries and/or any treatment side-effects you may have had.

We very much hope you will feel able to complete the enclosed questionnaire and return it in the pre-paid envelope – **no stamp is needed**.

Everything you tell us will be treated as **strictly confidential**. None of the information you give us will be passed on to anyone outside the study team. When the results of the study are presented, it will not be possible for individual patients to be identified in any way. You will see that we have also enclosed a pre-paid postcard which you can use in the future should you change your name or address, or now if we do not have your full details – again, no stamp is needed.

We will contact you again next year to see how things are for you then. We would like to take this opportunity to thank you once again for agreeing to help us with this important study.
Yours sincerely

Ann Jacoby
Professor of Medical Sociology

Appendix 3

Statistical analysis strategy for clinical outcomes

Descriptive analyses

Representativeness of study sample and patient throughput

Details of patients assessed for eligibility, those who meet the study inclusion criteria, those who are eligible and randomised, those who are eligible but not randomised, those who withdraw from the study after randomisation and those who are lost to follow-up will be summarised in a CONSORT flow diagram. Eligible patients who are randomised will be described with respect to demographic details and history [gender, age at randomisation, epilepsy syndrome, history (learning disability and neurological deficit), neurological disorder, history of seizures, number and timing of recent seizures]. Eligible non-randomised patients will be described similarly. The number of ineligible patients randomised will also be reported.

Baseline comparability of randomised groups

Patients in each treatment group (CBZ, GBP, LTG, OXC, TPM and VPS) in the two 'standard drug' arms (CBZ, Arm A; and VPS, Arm B) will be described separately with respect to gender, age at randomisation, treatment history, neurological disorder, history (learning disability and neurological deficit), history of seizures, epilepsy syndrome, interval between first and most recent seizure before randomisation (in days) and interval between most recent seizure and randomisation (in days) and total number of seizures ever. Tests of statistical significance will not be undertaken for baseline characteristics, rather the clinical importance of any imbalance will be noted.

Follow-up data and losses to follow-up

The number (and percentage) of patients attending scheduled follow-up visits at 3, 6, 12, 24, 36, 48 and 60 months (using windows of ±1 month, ±2 months, ±3 months, ±3 months, ±3 months, ±3 months, ±3 months) after randomisation will be reported and compared between treatment groups within each arm. Due to the time-to-event nature of the data it will be noted that information up to the date of last follow-up visit will be available for analyses. The number lost to follow-up within each treatment group will be reported and reasons where known will be documented. Any deaths and their causes will be reported separately.

Description of compliance with therapy

Deviations from intended drug (withdrawals from randomised drug or additional drugs initiated), withdrawal from study (due to withdrawal of consent or subsequent reclassification as 'Not epilepsy') will be summarised for treatment groups within each arm. Although compliance with AEDs is extremely difficult to measure, compliance-related items off QoL questionnaires will be summarised. For each treatment group within each arm a summary of the following will be provided: initial intended dose of randomised drug, maximum dose, and dose of randomised drug at or as near as possible to each event.

Patient groups for analysis

To provide a pragmatic comparison of the policies of the different drug treatments, the principle of intention-to-treat, as far as is practically possible, will be the main strategy of analysis adopted for the two primary end-points. Any patients reclassified as 'Not epilepsy' during the trial will be included in all analyses. These analyses will be conducted on all patients assigned to the treatment groups CBZ (Arm A), GBP (Arm A), LTG (Arm A), OXC (Arm A), TPM (Arm A), LTG (Arm B), TPM (Arm B), VPS (Arm B) as randomised. Due to the late inclusion of OXC, analyses and comparisons including OXC (Arm A only) will be based on data for patients randomised after the date of introduction of OXC only. Analyses for the remaining drugs in Arm A (CBZ, GBP, LTG, TPM) will be based on all randomised patients for the entire follow-up period. A sensitivity analysis, to examine the robustness of conclusions based on these latter results to the assumption that similar patient groups were recruited before and after the inclusion of OXC, will be undertaken. For this sensitivity analysis, results based on patients randomised to Arm A (CBZ, GBP, LTG, TPM) after the inclusion of OXC only will be compared with corresponding results based on patients recruited to these treatment groups over the entire

follow-up period. Analyses for arm B are unaffected by the inclusion of OXC and will include all patients randomised during the entire follow-up period.

Sensitivity analyses based on a 'per-protocol' (PP) analysis will be conducted to examine robustness of the main results to departure from intended trial treatment. For each outcome, patients reclassified as 'Not epilepsy' or who are found to fulfil any other trial exclusion criteria will be removed from the PP analyses. Due to the possibility that the outcomes may be experienced for a range of doses of each drug, patient exclusions based on dose will not be considered. The sample of patients for the PP analyses are defined for each outcome below:

(i) Time to withdrawal
  (a) Patients who did not receive the drug at all will be excluded
(ii) Time to first seizure
  (a) Patients who did not receive the drug at all will be excluded
  (b) Patients withdrawn from study or drug before first seizure will be censored at the date of withdrawal*
  (c) Patients with other AEDs added before their first seizure will be censored at the date of drug addition*
(iii) Time to 6 months, 12 months, 24 months remission
  (a) Patients who did not receive the drug at all will be excluded
  (b) Patients withdrawn from study or drug before achieving a period of remission (length of seizure-free period defined by outcome) will be censored at the date of withdrawal*
  (c) Patients with other AEDs added before achieving a period of remission (length of seizure free period defined by outcome) will be censored at the date of drug addition*

* The clinical and statistical issues of informative censoring for the PP analyses have been identified. The problem arises for the remission outcomes as follows: if seizure-related withdrawals (withdrawals from study or drug prior to achievement of a period of remission) or drug additions (additional AED added prior to achievement of a period of remission) are censored at the date of withdrawal (date withdrawal started) or addition, the underlying assumption that time to achieve remission for an individual is independent of any mechanism which causes that individual's time to be censored at some time is violated. The problem arises for the first seizure outcome as follows: if withdrawals or drug additions occur before first seizure such events are likely to be caused by the randomised drug taken at a high dose. A high dose of randomised drug is also likely to increase the time taken to first seizure, therefore the underlying assumption that time to first seizure for an individual is independent of any mechanism which causes that individual's time to be censored at some time is again violated.

Analysis of primary outcomes

Outcome measures

There are two primary clinical outcome measures:

(a) time from randomisation to intention to withdraw the randomised drug due to lack of efficacy (poor seizure control) and/or intolerable side-effects; or the addition of other AEDs, whichever is the earliest;
(b) time from randomisation to the achievement of a period of one year remission (defined as complete absence of seizures of any type).

For these primary outcomes, a p-value of 0.05 (5% level) will be used to declare statistical significance.

Comparison of first primary outcome (withdrawal or addition) between groups

For the analysis of time to withdrawal or addition, an event is defined as the withdrawal of randomised drug and/or the addition of other AEDs due to inadequate seizure control and/or unacceptable adverse events and/or non-compliance. Time to withdrawal or addition is calculated by subtracting the date of randomisation from the date of intention to withdraw (date that withdrawal began) or add new AED (date at which the first dose of other AEDs began), whichever is earliest.

If withdrawal from or addition to randomised drug occurs due to remission of epilepsy, or because the diagnosis is no longer epilepsy, or for some other reason not related to drug treatment, the time to withdrawal or addition will be censored at the time that withdrawal from or addition to randomised drug began. If the patient moves from the area or is lost to follow-up, the time to withdrawal or addition will be censored at the last known date of follow-up. Full details of the event/censoring classification system for this outcome are given in *Table 80*.

If withdrawal or addition does not take place at any time during the follow-up period, time to withdrawal or addition is calculated by subtracting date of randomisation from the date of last follow-up and the outcome is censored.

Withdrawals from and additions to randomised drug will be reported as numbers (and percentages) of patients with reasons for withdrawal or addition for each treatment group in each arm. For each arm separately, the interval (in days) from randomisation to withdrawal or addition will be summarised by Kaplan–Meier curves for each treatment group and compared overall using a log-rank test. The Cox model will then be fitted; three different models will be used: (i) including the treatment effect only using treatment indicator variables; (ii) including the treatment effect together with pre-stratification (design) factors [centre, sex, treatment history (three categories)]; and (iii) adjusting both for pre-stratification factors as well as the following post-stratification baseline factors: age at randomisation, presence of neurological signs, seizure type (partial onset, generalised onset or unclassified), number of seizures prior to randomisation, time from first ever seizure to randomisation (days), EEG results (normal/abnormal) and CT/MRI scan results (normal/abnormal). Hazard ratios (and 95% CIs) for withdrawal or addition in each treatment group in the two arms will be summarised in a table. The assumption of proportional hazards for the treatment effect in the Cox model will be checked using a time-dependent covariate.

Comparison of second primary outcome (12-month remission) between groups

For the analysis of time to 12-month remission, an event is defined as a period of at least 12 months that is free from all types of seizure. If the event is achieved, the date of 12-month remission is taken as exactly 12 months from the date of last seizure, or date of randomisation if no seizures occurred. Time to achieve a period of 12-month remission is calculated by subtracting randomisation date from this date. If the event is not achieved, time to 12-month remission is calculated by subtracting date of randomisation from the date of last follow-up and the outcome is censored.

For each arm separately, the interval (in days) from randomisation to attainment of 12-month remission will be summarised by Kaplan–Meier curves for each treatment group and compared overall using a log-rank test. The Cox model will then be fitted; three different models will be used: (i) including the treatment effect only using treatment indicator variables; (ii) including the treatment effect together with pre-stratification (design) factors [centre, sex, treatment history (three categories)]; and (iii) adjusting both for pre-stratification factors as well as the following post-stratification baseline factors: age at randomisation, presence of neurological signs, seizure type (partial onset, generalised onset or unclassified), number of seizures prior to randomisation, time from first ever seizure to randomisation (days), EEG results (normal/abnormal) and CT/MRI scan results (normal/abnormal). Hazard ratios (and 95% CIs) for remission in each treatment group in the two arms will be summarised in a table. The assumption of proportional hazards for the treatment effect in the Cox model will be checked using a time-dependent covariate.

Tests of interaction between baseline characteristics and treatment

Treatment-covariate interactions may be examined in exploratory analyses reported in subsequent papers. The interaction of primary clinical importance is between seizure type (partial onset, generalised onset or unclassified) and treatment. However, the number of patients available and the power to detect an interaction are anticipated to be very low due to the trial design. Further interactions between treatment and the following factors will be explored using training and validation data sets: age at randomisation, presence of neurological signs, number of seizures prior to randomisation, time from first ever seizure to randomisation (days), EEG results (normal/abnormal) and CT/MRI scan results (normal/abnormal).

Analysis of secondary outcomes

Four secondary clinical outcome measures are of interest:

(a) time from randomisation to first seizure of any type
(b) time from randomisation to achieve a period of 6-month remission
(c) time from randomisation to achieve a period of 24-month remission
(d) incidence of clinically important events and side-effects emerging within defined periods after randomisation (3 months, 6 months, 12 months and annually thereafter).

For the secondary outcomes, a p-value of 0.05 (5% level) will be used to declare statistical significance

TABLE 80 *Categorising events and censoring for time to treatment failure*

Reason for withdrawal from drug/study or other drug addition (earliest event)	Categorised as event or censored in 'time to withdrawal or addition' analysis
Inadequate seizure control	Event
Unacceptable adverse events	Event
Remission of epilepsy categorised by clinician (regardless of length in remission)	Censored
Remission of epilepsy categorised by patient (MORE than 12 months remission from seizures)	Censored
Remission of epilepsy categorised by patient[a] (LESS than 12 months remission from seizures)	Event
Not epilepsy	Censored
Study withdrawal - Consent withdrawn[b]	Censored
Death (unrelated to epilepsy/AED)[c]	Censored
Death (related to epilepsy/AED)[c]	Event
Moved from area	Censored
Patient non-compliant/did not wish to continue[d]	Event
Perceived adverse effect, e.g. pregnant or planning pregnancy	Event

[a] A patient's decision to withdraw before 12 months' freedom from seizures is likely to be highly influenced by side-effects or perception of side-effects.
[b] Study withdrawals are automatically checked to ensure that the patient wants to withdraw from study rather than from drug only.
[c] Blinded assessment to identify whether death is related or unrelated to epilepsy/AED to take place prior to analysis.
[d] Further information is to be sought if patient withdraws from drug due to "non-compliance" as the underlying reason could be unacceptable adverse events, inadequate seizure control **OR** remission of epilepsy. If further information is unavailable sensitivity analyses will be performed first coding non-compliance as event then second as a censored observation.

with relevant results from other studies already reported in the literature also taken into account; a p-value of 0.01 (1% level) will be used to declare statistical significance in analyses that are purely exploratory.

For each arm separately, the interval (in days) from randomisation to first seizure of any type will be summarised by Kaplan–Meier curves for each treatment group and compared overall using a log-rank test. The Cox model will then be fitted; three different models will be used: (i) including the treatment effect only using treatment indicator variables; (ii) including the treatment effect together with pre-stratification (design) factors [centre, sex, treatment history (three categories)]; and (iii) adjusting both for pre-stratification factors as well as the following post-stratification baseline factors: age at randomisation, presence of neurological signs, seizure type (partial onset, generalised onset or unclassified), number of seizures prior to randomisation, time from first ever seizure to randomisation (days), EEG results (normal/abnormal) and CT/MRI scan results (normal/abnormal). Hazard ratios (and 95% CIs) for seizure in each treatment group in the two arms will be summarised in a table. The assumption of proportional hazards for the treatment effect in the Cox model will be checked using a time-dependent covariate.

Side-effects will be grouped according to a pre-specified side-effect coding system and tabulated. The number (and percentage) of patients experiencing each side-effect will be compared across treatment groups within each arm. The number (and percentage) of occurrences of each side-effect will also be compared across treatment groups within each arm. No formal statistical test will be undertaken.

Acknowledgement

We would like to thank investigators from the MRC Multicentre Randomised Controlled Trial of

Cognitive Therapy for Bipolar Affective Disorder for making their statistical analysis strategy document available as a template for the current strategy.

If a patient records a combination of reasons, e.g. moved from area then decided to come off treatment because of rash, then if any event defining reason is included in the description we would classify as event. Otherwise we would censor.

Appendix 4

Collaborators and trial management committees

SANAD Study Group members

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Quality of Life Study Coordinator – Prof. A Jacoby (Liverpool)
Health Economics Coordinator – Dr P Shackley, Ms A Vanoli, Ms J Shen (Newcastle)
Statistical Coordinator – Prof. P Williamson (Liverpool)
Trial Statisticians – Dr C Tudur-Smith, Dr C Gamble (Liverpool)
Neuropsychology Study Coordinator – Prof. G Baker (Liverpool)
DNA Bank Coordinator – Dr MR Johnson (Imperial College, London)
Trial Administration Liverpool – Mrs B Eaton, Ms T Ball, Mrs H Crone
Trial Administration Newcastle – Ms J Doughty, Ms J Dryburgh, Ms P Potts, Mrs V Swain-Dixon, Mrs L Wake
DNA Bank Administration – Ms C Middleditch
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Manchester Randomisation Centre from 01 January 1999 to 31 August 2003 – Dr Dey

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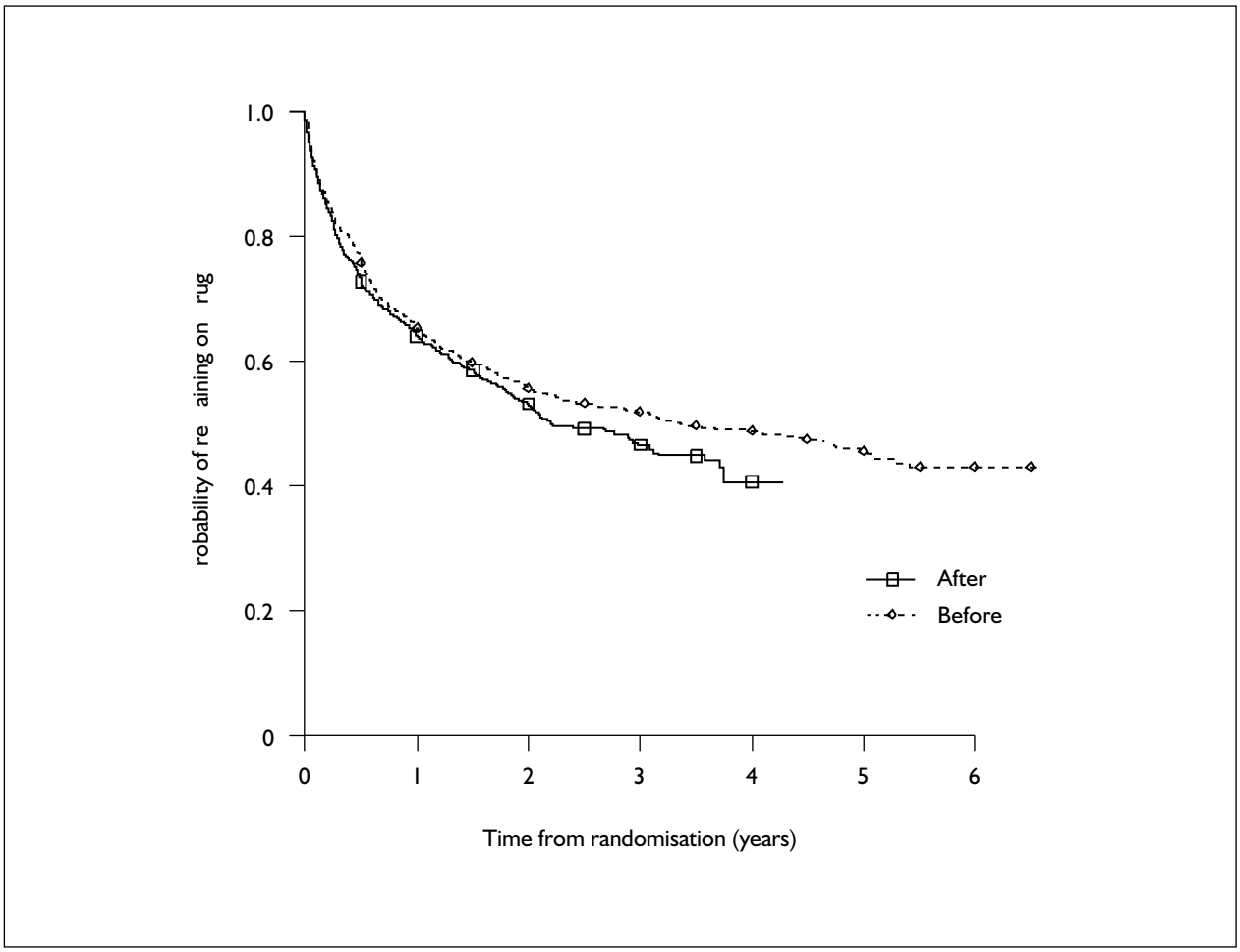
Appendix 5

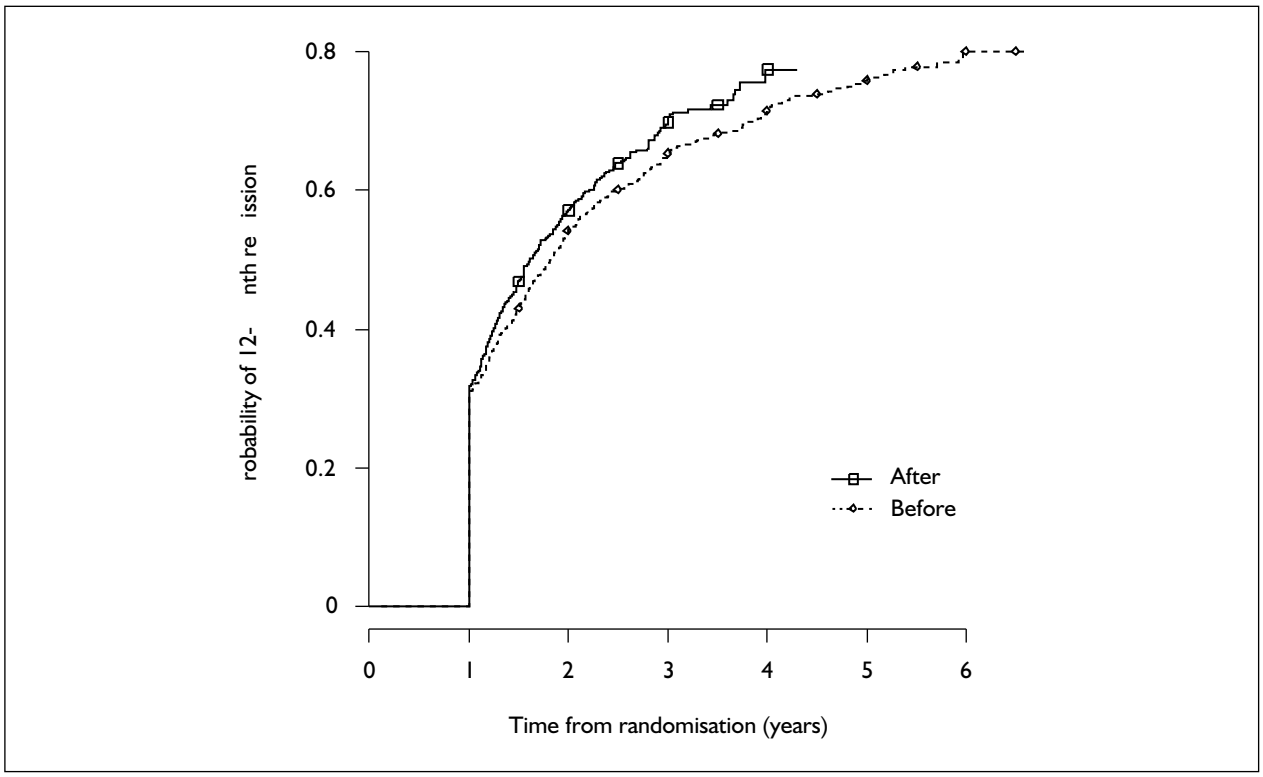
Consideration of outcomes for drugs excluding oxcarbazepine before and after June 2001

Relevant data are presented in *Figures 58–61*.



Recruitment	Events	Total
Before June 2001	340	668
After June2001	403	838
Total	743	1506
Log-rank analysis, $\chi^2 = 2.677$, df = 1, $p = 0.102$.		

FIGURE 58 *Time to treatment failure (Arm A) comparing recruitment before and after June 2001 (excluding OXC) (entire recruitment period)*



Recruitment	Events	Total
Before June 2001	472	653
After June2001	482	821
Total	954	1474
Log-rank analysis, $\chi^2 = 2.876$, df = 1, $p = 0.090$.		

FIGURE 59 *Time to 12 month remission (Arm A) comparing recruitment before and after June 2001 (excluding OXC) (entire recruitment period)*

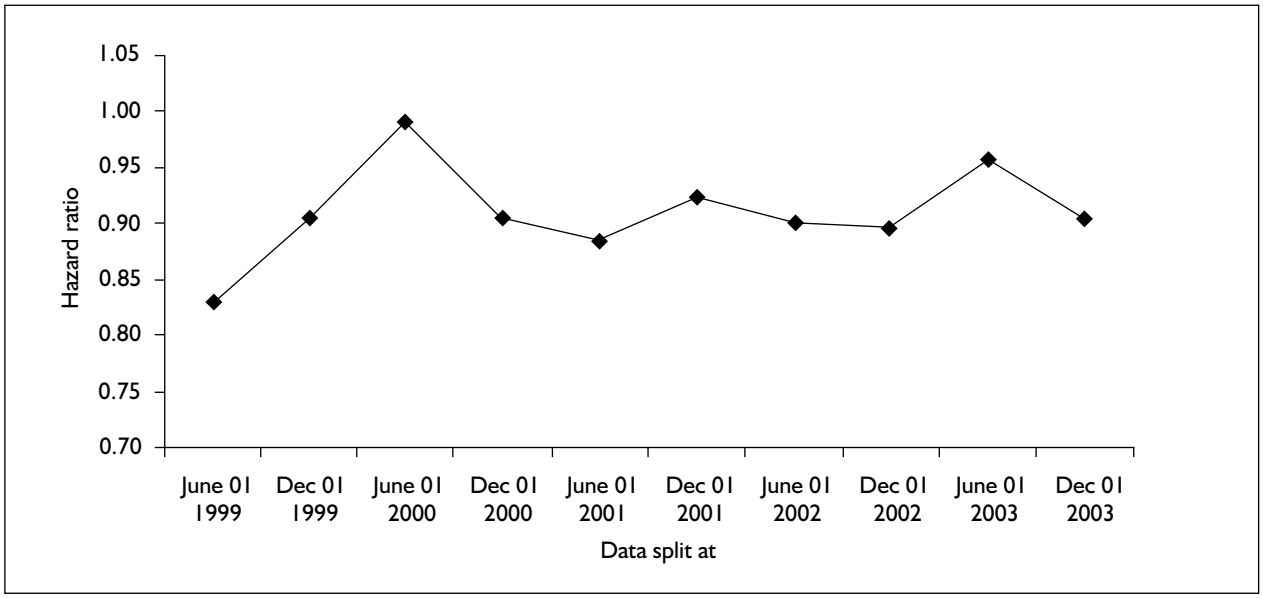


FIGURE 60 *Hazard ratios for time to treatment failure (Arm A) comparing recruitment before and after each data split (excluding OXC) (entire recruitment period)*

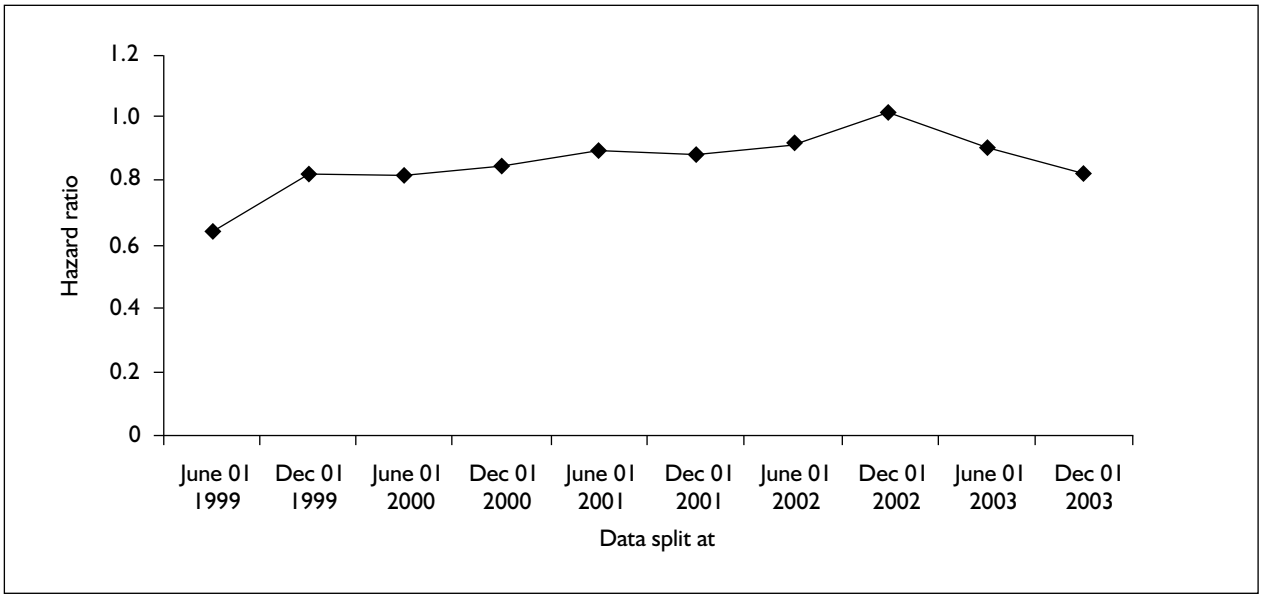


FIGURE 61 *Hazard ratios for time to 12-month remission (Arm A) comparing recruitment before and after each data split (excluding OXC) (entire recruitment period)*

It can be seen that there are some differences in outcomes between the two recruitment periods divided by 1 June 2001. There appears to be a trend towards greater hazard for treatment failure but also for an increased likelihood of achieving a 12-month remission of seizures, neither of which reach statistical significance. Further analyses were undertaken comparing primary outcomes for each drug treatment group divided by recruitment before or after 1 June 2001 (*Tables 81* and *82*).

Because of the absence of any consistent pattern for outcomes for individual drugs when comparisons were made between patients randomised before and after 1 June 2001, an exploratory analysis of individual drug dosing in the two periods was undertaken (*Table 83*).

It would not appear from this that there are systematic differences in planned initial doses for drugs between the two periods sufficient to explain variations in outcomes for either individual drugs or the entirety of patients randomised before or after June 2001. We therefore compared patient characteristics for the samples recruited before and after June 2001. This shows that the percentage of patients recruited before June 2001 who had a history of previous failure on monotherapy was higher than after June 2001 (21% versus 12%), as were the percentages of patients with a history of learning disability and neurological deficit (17% versus 11%) and percentages of patients with previous neurological disorder (27% versus 22%). This suggests that collaborators may well have been

TABLE 81 *Summary of analyses for Arm A – time to treatment failure for each individual drug*

Description	Number of events/total	Log-rank test (overall) χ^2 (df), *p*-value
Time to treatment failure Comparing before and after – Arm A, CBZ	177/378	0.034 (1), $p = 0.8534$
Time to treatment failure Comparing before and after – Arm A, GBP	209/376	4.467 (1), $p = 0.035$
Time to treatment failure Comparing before and after – Arm A, LTG	155/378	3.921 (1), $p = 0.048$
Time to treatment failure Comparing before and after – Arm A, TPM	202/374	0.836 (1), $p = 0.361$

TABLE 82 *Summary of analyses for Arm A – time to 12-month remission each individual drug*

Description	Number of events/total	Log-rank test (overall) χ^2 (df) *p*-value
Time to 12-month remission Comparing before and after – Arm A, CBZ	261/371	4.025 (1), $p = 0.045$
Time to 12-month remission Comparing before and after – Arm A, GBP	217/367	0.020 (1), $p = 0.888$
Time to 12-month remission Comparing before and after – Arm A, LTG	248/371	0.087 (1), $p = 0.769$
Time to 12-month remission Comparing before and after – Arm A, TPM	228/365	2.488 (1), $p = 0.115$

TABLE 83 *Arm A – planned maintenance dose before and after OXC introduced*

Recruitment	CBZ	GBP	LTG	TPM
Before June 2001	($n = 167$)	($n = 167$)	($n = 168$)	($n = 168$)
Mean (standard deviation) range	593 (116) 200–1000	1270 (330) 400–3200	185 (51) 75–400	165 (58) 30–400
After June 2001	($n = 211$)	($n = 210$)	($n = 210$)	($n = 210$)
Mean (standard deviation) range	598 (130) 200–1200	1311 (341) 400–2400	172 (50) 50–400	151 (52) 50–400

recruiting initially from a pool of patients with poorer prognosis and greater prior experience of AED therapy. However, when the treatment failure and 12-month remission outcomes were considered, the differences in outcome persisted when comparison between the two periods was restricted to the patients previously untreated at randomisation.

Appendix 6

QoL analysis. Hotdecked imputations (Arm A only)

Two-year data for participants returning a baseline but not a 2-year questionnaire were imputed using a hotdeck technique[87] for the CBZ arm only. Where the reason for missing data was pending/not due, imputations have not been performed (since this reason for being missing should not bias results).

For each participant with a missing 2-year questionnaire, a hotdeck was created consisting of a participant who had responded at 2 years, matched on remission and withdrawal during the 2-year clinical follow-up, anxiety and depression status at baseline (defined as ordered categorical outcome), sex and age group at randomisation (<30, 30–<50, ≥50 years). If no matching participants were identified from the 2-year responders, then the matching criteria were relaxed in the order age group, sex, depression, anxiety, AED withdrawal, until a match was identified. The aim of this imputation approach is to consider the robustness of the results to the responder bias. This approach has two main limitations: first, it assumes the imputed data are known, thereby increasing the precision of the estimates from the hotdecked data set in comparison with the data set with missing data; second, due to the size of this dataset, it was not possible to restrict matching to participants randomised to the same treatment group – so, for example, a person randomised to LTG with missing data at 2 years could have their values imputed by a person randomised to GBP who responded at 2 years.

Numbers included in the analysis following hotdecking are provided in *Table 84* (in italics, with comparison figures for the original analysis in parentheses). Hotdecking increased the available data set by between 24 and 68 participants.

Tables 85–90 present hotdecked scores (with 95% CIs) for the core QoL measures at 2 years by treatment group adjusted for baseline values. As previously, in each table columns represent the baseline comparator: for example, in the CBZ

TABLE 84 *Number of participants per group after hotdecking*

	CBZ	GBP	LTG	TPM	OXC
CBZ arm whole period	*262* (195)	*260* (197)	*241* (177)	*240* (172)	
CBZ arm after the including OXC	*141* (107)	*145* (121)	*130* (92)	*124* (90)	*130* (92)

TABLE 85 *Two-year anxiety scores after hotdecking*[a]

	CBZ	GBP	LTG	TPM	OXC
CBZ	–	*0.01 (–0.71 to 0.68)* 0.01 (–0.76 to 0.78)	*0.13 (–0.58 to 0.83)* 0.09 (–0.70 to 0.88)	*0.22 (–0.49 to 0.93)* 0.84 (0.04 to 1.63)	*0.04 (–0.91 to 0.99)* –0.13 (–1.10 to 0.83)
GBP	*–0.01 (–0.68 to 0.71)* –0.01 (–0.78 to 0.76)	–	*0.14 (–0.57 to 0.85)* 0.08 (–0.71 to 0.87)	*0.23 (–0.48 to 0.95)* 0.83 (0.03 to 1.62)	*–0.18 (–1.12 to 0.76)* –0.15 (–1.11 to 0.81)
LTG	*–0.13 (–0.83 to 0.58)* –0.09 (–0.88 to 0.70)	*–0.14 (–0.85 to 0.57)* –0.08 (–0.87 to 0.71)	–	*0.09 (–0.63 to 0.82)* 0.75 (–0.07 to 1.56)	*–0.74 (–1.70 to 0.22)* –0.23 (–1.21 to 0.76)
TPM	*–0.22 (–0.93 to 0.49)* –0.84 (–1.63 to –0.04)	*–0.23 (–0.95 to 0.48)* –0.83 (–1.62 to –0.03)	*–0.09 (–0.82 to 0.63)* –0.75 (–1.56 to 0.07)	–	*–0.54 (–1.52 to 0.44)* –0.97 (–1.96 to 0.01)

[a] In this and the following tables, hotdecked results are shown in italic and original (non-hotdecked) results are shown in roman font.

TABLE 86 *Two-year depression scores after hotdecking*

	CBZ	GBP	LTG	TPM	OXC
CBZ	–	*–0.22 (–0.80 to 0.37)* –0.28 (–0.94 to 0.37)	*0.49 (–0.11 to 1.09)* 0.35 (–0.33 to 1.02)	*–0.04 (–0.64 to 0.57)* –0.09 (–0.77 to 0.59)	*0.09 (–0.69 to 0.87)* –0.29 (–1.11 to 0.53)
GBP	*0.22 (–0.37 to 0.80)* 0.28 (–0.37 to 0.94)	–	*0.70 (0.10 to 1.30)* 0.63 (–0.04 to 1.30)	*0.18 (–0.43 to 0.78)* 0.19 (–0.48 to 0.86)	*0.10 (–0.66 to 0.87)* –0.01 (–0.82 to 0.81)
LTG	*–0.49 (–1.09 to 0.11)* –0.35 (–1.02 to 0.33)	*–0.70 (–1.30 to –0.10)* –0.65 (–1.30 to 0.04)	–	*–0.52 (–1.14 to 0.09)* –0.44 (–1.13 to 0.25)	*–0.78 (–1.57 to 0.01)* –0.63 (–1.47 to 0.20)
TPM	*0.04 (–0.57 to 0.64)* 0.09 (–0.59 to 0.77)	*–0.18 (–0.78 to 0.43)* –0.19 (–0.86 to 0.48)	*0.52 (–0.09 to 1.14)* 0.44 (–0.25 to 1.12)	–	*–0.19 (–0.99 to 0.62)* –0.20 (–1.04 to 0.64)

TABLE 87 *Two-year AEP scores after hotdecking*

	CBZ	GBP	LTG	TPM	OXC
CBZ	–	*–0.32 (–2.05 to 1.41)* –0.60 (–2.34 to 1.15)	*–0.30 (–2.11 to 1.51)* –0.47 (–2.32 to 1.38)	*–0.46 (–2.25 to 1.33)* 0.60 (–1.23 to 2.42)	*0.60 (–1.73 to 2.92)* 0.45 (–1.83 to 2.72)
GBP	*0.32 (–1.41 to 2.05)* 0.60 (–1.15 to 2.34)	–	*0.02 (–1.80 to 1.84)* 0.13 (–1.72 to 1.97)	*–0.14 (–1.94 to 1.65)* 1.19 (–0.62 to 3.01)	*–0.51 (–2.84 to 1.81)* 1.04 (–1.23 to 3.32)
LTG	*0.30 (–1.51 to 2.11)* 0.47 (–1.38 to 2.32)	*–0.02 (–1.84 to 1.80)* –0.13 (–1.97 to 1.72)	–	*–0.16 (–2.03 to 1.71)* 1.07 (–0.85 to 2.99)	*–0.76 (–3.23 to 1.72)* 0.91 (–1.44 to 3.26)
TPM	*0.46 (–1.33 to 2.25)* –0.60 (–2.42 to 1.23)	*0.14 (–1.65 to 1.94)* –1.19 (–3.01 to 0.62)	*0.16 (–1.71 to 2.03)* –1.07 (–2.99 to 0.85)	–	*1.08 (–1.42 to 3.57)* –0.15 (–2.48 to 2.19)

TABLE 88 *Two-year neurotoxicity scores after hotdecking*

	CBZ	GBP	LTG	TPM	OXC
CBZ	–	*1.83 (–0.91 to 4.57)* 0.12 (–2.63 to 2.86)	*2.77 (–0.02 to 5.57)* 1.30 (–1.57 to 3.93)	*–0.01 (–2.82 to 2.81)* 1.58 (–1.27 to 4.42)	*0.45 (–3.28 to 4.18)* –0.72 (–4.12 to 2.68)
GBP	*–1.83 (–4.57 to 0.91)* –0.12 (–2.86 to 2.63)	–	*0.95 (–1.82 to 3.71)* 1.18 (–1.57 to 3.93)	*–1.84 (–4.63 to 0.96)* 1.48 (–1.32 to 4.28)	*–2.83 (–6.49 to 0.84)* –0.79 (–4.15 to 2.57)
LTG	*–2.77 (–5.57 to 0.02)* –1.30 (–4.09 to 1.50)	*–0.95 (–3.71 to 1.82)* –1.18 (–3.93 to 1.57)	–	*–2.78 (–5.62 to 0.06)* 0.30 (–2.54 to 3.14)	*–3.65 (–7.42 to 0.12)* –1.98 (–5.38 to 1.42)
TPM	*0.01 (–2.81 to 2.82)* –1.60 (–4.43 to 1.24)	*1.84 (–0.96 to 4.62)* –1.48 (–4.28 to 1.32)	*2.78 (–0.06 to 5.62)* –0.30 (–3.14 to 2.54)	–	*–0.67 (–4.52 to 3.18)* –2.29 (–5.73 to 1.15)

column, scores are for the other groups **compared with** CBZ. Also as previously, all columns other than the OXC column are for the whole period, whereas in the latter scores are for the other groups compared with OXC for the period after the inclusion of OXC only. Values for continuous measures are the coefficients from a multiple regression representing the difference between treatments, with 95% CIs. Values for ordinal measures are the exponentiated coefficients from a proportional odds model, with 95% CIs, such that the values represent the odds of increasing severity of outcome.

As for the non-hotdecked analyses, few differences in QoL between treatment groups were identified, although some trends in the data were evident. Thus, based both on mean scores (*Table 85*) and 'caseness' (*Table 90*), there was a small and non-significant reduction in risk of anxiety for both LTG and TPM, compared with CBZ, GPB and OXC; there was a trend (for caseness only) for reduced risk of depression for LTG and increased depression for GBP compared with the other drugs (*Table 86*), but the difference no longer reached statistical significance for LTG compared to GBP. There were no important differences or

TABLE 89 *Two-year EQ-5D scores after hotdecking*

	CBZ	GBP	LTG	TPM	OXC
CBZ	–	*0.00 (–0.04 to 0.05)* –0.01 (–0.06 to 0.04)	*0.00 (–0.04 to 0.05)* –0.02 (–0.06 to 0.03)	*–0.01 (–0.05 to 0.04)* –0.03 (–0.08 to 0.02)	*–0.00 (–0.06 to 0.05)* 0.01 (–0.05 to 0.07)
GBP	*–0.00 (–0.05 to 0.04)* 0.01 (–0.04 to 0.06)	–	*0.00 (–0.04 to 0.05)* –0.01 (–0.05 to 0.04)	*–0.01 (–0.05 to 0.04)* –0.02 (–0.07 to 0.03)	*0.01 (–0.05 to 0.07)* 0.02 (–0.04 to 0.08)
LTG	*–0.00 (–0.05 to 0.04)* 0.02 (–0.03 to 0.06)	*–0.00 (–0.05 to 0.04)* 0.01 (–0.04 to 0.05)	–	*–0.01 (–0.06 to 0.04)* –0.01 (–0.06 to 0.04)	*0.01 (–0.05 to 0.06)* 0.03 (–0.03 to 0.08)
TPM	*0.01 (–0.04 to 0.05)* 0.03 (–0.02 to 0.08)	*0.01 (–0.04 to 0.05)* 0.02 (–0.03 to 0.07)	*0.01 (–0.04 to 0.06)* 0.01 (–0.04 to 0.06)	–	*0.03 (–0.03 to 0.09)* 0.04 (–0.02 to 0.10)

TABLE 90 *Two-year anxiety scores (ordinal) after hotdecking*

	CBZ	GBP	LTG	TPM	OXC
CBZ	–	*0.99 (0.68 to 1.45)* 0.98 (0.63 to 1.53)	*1.12 (0.76 to 1.64)* 1.04 (0.66 to 1.65)	*1.13 (0.76 to 1.66)* 1.60 (1.01 to 2.60)*	*0.93 (0.55 to 1.57)* 1.02 (0.58 to 1.79)
GBP	*1.01 (0.69 to 1.48)* 1.02 (0.65 to 1.59)	–	*1.13 (0.77 to 1.66)* 1.06 (0.67 to 1.68)	*1.14 (0.77 to 1.68)* 1.65 (1.03 to 2.65)*	*1.06 (0.63 to 1.77)* 1.03 (0.59 to 1.82)
LTG	*0.90 (0.61 to 1.32)* 0.96 (0.61 to 1.52)	*0.89 (0.60 to 1.31)* 0.94 (0.60 to 1.49)	–	*1.01 (0.68 to 1.50)* 1.55 (0.96 to 2.53)	*0.73 (0.43 to 1.25)* 0.98 (0.55 to 1.75)
TPM	*0.89 (0.60 to 1.31)* 0.62 (0.38 to 0.99)	*0.88 (0.59 to 1.30)* 0.61 (0.38 to 0.98)	*0.99 (0.67 to 1.48)* 0.64 (0.40 to 1.05)	–	*0.71 (0.41 to 1.24)* 0.64 (0.35 to 1.15)

trends for scores on the AEP, the Neurotoxicity Scale, the EQ-5D or for GQoL. Comparison of the hotdecked and non-hotdecked results is therefore reassuring in suggesting that non-response biases may not be major in their effects (although the inability to match patients by randomised drug means that caution must be applied to this conclusion).

Appendix 7

Response rates to the QoL study

In this appendix, we provide information about baseline and 2-year follow-up response rates and the characteristics of responders versus non-responders, for the entire population of patients recruited to the QoL study. This is important, since our analysis showed that there was clear responder bias, in terms of both patient characteristics and their baseline QoL profiles, and this has potential implications for interpretation of the QoL outcomes data. Since there is also evidence[88,89] that late responders to postal questionnaires more closely resemble non-responders than early respondents, we also present information about the speed of response for those doing so.

Overall response rates and reasons for non-response

In survey research, response rates to postal questionnaires of between 70 and 85% are considered acceptable to very good.[90,91] In SANAD, 1911 of the 1983 adult participants randomised to the clinical study were sent a baseline QoL questionnaire, of whom 30 subsequently were found not to have epilepsy and so were excluded from the analysis. Of the remaining 1881, 1587 (84.4%) responded and 294 (15.6%) did not. Reasons for non-response are given in *Table 91*.

TABLE 91 *Reasons for non-response at baseline*

Reasons	Frequency	%
Non-English speaker	1	0.34
Died/too ill[a]	10	3.40
Withdrew from study[b]	18	6.12
Refused[c]	29	9.86
Non-contact[d]	62	21.09
Non-response[e]	174	59.18

[a] Of the 10 classified as died/too ill there were 5 deaths (all non-epilepsy) at days 23, 61, 89, 109 and 147 after randomisation.
[b] Withdrew from the study = withdrew from both clinical and QoL study.
[c] Refused = contact made and participant stated they did not want to complete the QoL questionnaire or receive future questionnaires.
[d] Non-contact = unable to establish whether participant actually received QoL questionnaire.
[e] Non-response = confirmed that participant received the questionnaire, but they did not respond.

TABLE 92 *Reasons for non-response at 2 years*

Reason	Frequency	%
Emigrated	2	0.47
Epilepsy-related death	4	0.94
Non-epilepsy-related death	17	3.99
Too ill	24	5.63
Withdrew from study	25	5.87
Refused	53	12.44
Non-contact	115	27.00
Non-response	186	43.66

At the 2-year follow-up, 1058 adult participants responded. Of these, 16 returned a QoL questionnaire at 2 years but not at baseline (participants received follow-up questionnaires if they had responded either at baseline or at 3 months). Hence data are available at both baseline and 2 years for 1042 participants. Of the 545 (1587 – 1042) with no 2-year data, the 2-year follow-up time point or response were not due or were pending in 119 participants (cut-off point for the analysis was end-February 2006) – leaving 426 (29%) non-responders at 2 years. Reasons for non-response are given in *Table 92*.

Characteristics of responders and non-responders

Differences between the characteristics of responders and non-responders were identified both at baseline and at 2-year follow-up (*Tables 93–95*). Females were more likely to respond to the questionnaires than males, and the median age for responders was higher than for non-responders.

Of the 1587 adult participants who returned a questionnaire at baseline, differences were identified between those who subsequently returned a 2-year follow-up questionnaire and those who did not for the QoL measures defined as core and so the focus of the present analysis

TABLE 93 *Response at baseline by gender*

	Response at baseline[a]	
	Female	**Male**
No response	102 (14%)	191 (19%)
Responder	650 (86%)	799 (81%)
Total	752	990

χ^2 p-value = 0.0015.
[a] Excludes 1 participant at baseline who did not respond due to being non-English-speaking.

TABLE 94 *Response at 2 years by gender*

	Response at 2 years (restricted to responders at baseline)[a]	
	Female	**Male**
No response	157 (24%)	250 (31%)
Responder	493 (76%)	549 (69%)
Total	650	799

χ^2 p-value = 0.0026.
[a] Excludes 138 who did not respond at 2 years for reasons pending/not due (119), non-epilepsy death (17) or emigrated (2).

TABLE 95 *Age of responders and non-responders at baseline and 2 years*

	Age (years): median (LQR, UQR)		
	Non-responders	**Responders**	***p*-Value**
Response at baseline	31.6 (22.9 to 44.7)	37.6 (26.5 to 52.6)	0.0026
Response at 2 years (restricted to responders at baseline)	32.2 (22.6 to 45.2)	40.4 (29.1 to 55.1)	<0.0001

LQR, lower quartile range, UQR, upper quartile range.

TABLE 96 *Comparison of baseline QoL scale scores for those responding at 2 years compared with those not responding at 2 years*

Outcome measure	**Score range**	**No response at 2 years[a] (n = 407)**	**Response at 2 years (n = 1042)**	***p*-Value[b]**
Anxiety (median score)	0–21, 0 = not anxious	9 (5–13) (n = 393)	7 (3–11) (n = 1018)	<0.0001
Anxiety caseness:				
Not anxious	0–7 = not a case,	(n = 393)	(n = 1018)	<0.0001
Borderline	8–10 = borderline,	162 (41%)	539 (53%)	
Anxious	⩾11 = a case	63 (16%)	192 (19%)	
		168 (43%)	287 (28%)	
Depression (median score)	0 to 21, 0 = not depressed	6 (3–10) (n = 396)	4.5 (2–8) (n = 1028)	<0.0001
Depression caseness:	0–7 = not a case,	(n = 396)	(n = 1028)	<0.0001
Not depressed	8–10 = borderline,	233 (59%)	730 (71%)	
Borderline	⩾11 = a case	79 (20%)	177 (17%)	
Depressed		84 (21%)	121 (12%)	
Neurotoxicity (median score)	0–72, 0 = no problems	21 (9–37) (n = 375)	14 (5–29) (n = 949)	<0.0001
Adverse events profile (median score)	0–57, 0 = no adverse events	43 (34–50) (n = 357)	39 (31–48) (n = 944)	<0.0001
EQ-5D (median score)	0–1 with 1 being full health	0.81 (0.59–1.0) (n = 389)	0.85 (0.69–1.0) (n = 1014)	<0.0001
GQoL (Terrible–Delighted Faces Scale):	1–7, 1 = best possible QoL, 7 = worst possible QoL	(n = 401)	(n = 1019)	<0.0001
1 (best)		32 (8%)	96 (9%)	
2		56 (14%)	197 (19%)	
3		106 (26%)	187 (18%)	
4		78 (20%)	128 (13%)	
5		69 (17%)	59 (6%)	
6		38 (9%)	30 (3%)	
7 (worst)		22 (5%)		

[a] Excludes 138 with baseline data but no response at 2 years for the following reasons: QoL questionnaire pending/not due (119); patient emigrated (2); non-epilepsy-related death (17).
[b] For continuous data, results are medians (interquartile ranges) and test of significance is Wilcoxon test; for categorical data, test of significance is χ^2 for trend.

TABLE 97 *Comparison of 2-year clinical outcome for those responding at 2 years compared with those not responding at 2 years: achieved a 12-month remission or not*

	Not in remission after 2 years follow-up	In remission after 2 years follow-up	Total
No response at 2 years	207 (52%)	191 (48%)	398
Responded at 2 years	404 (39%)	638 (61%)	1042
Total	611	829	
χ^2 *p*-value <0.0001.			

TABLE 98 *Comparison of 2-year clinical outcome for those responding at 2 years compared with those not responding at 2 years: withdrawal of initial drug or not*

	Not withdrawn from AED during 2 years follow-up	Withdrawn from AED during 2 years follow-up	Total
No response at 2 years	209 (52%)	195 (48%)	404
Responded at 2 years	649 (62%)	393 (38%)	1042
Total	858	588	
χ^2 *p*-value = 0.0002.			

(anxiety, depression, neurotoxicity, other AED adverse effects, EQ-5D scores and self-rated GQoL). Non-responders at 2 years were found to report worse baseline levels of anxiety and depression, higher neurotoxicity and adverse events, poorer EQ-5D scores and poorer GQoL (*Table 96*). Two-year non-responders were also less likely to have achieved a 12-month remission of seizures prior to the 2-year follow up, and were more likely to have been withdrawn from the drug to which they were allocated at randomisation (*Tables 97* and *98*).

Speed of return of QoL questionnaires by responders

For a questionnaire to represent a 'true' baseline assessment, it should be completed as close as possible to the randomisation date. In SANAD, as described in Chapter 2, questionnaires were mailed to participants as early as possible after (in most cases within 7–14 days) randomisation; however, there was considerable variability in the speed with which the 1587 responding participants then returned them (*Figure 62*). Of the 1042 participants

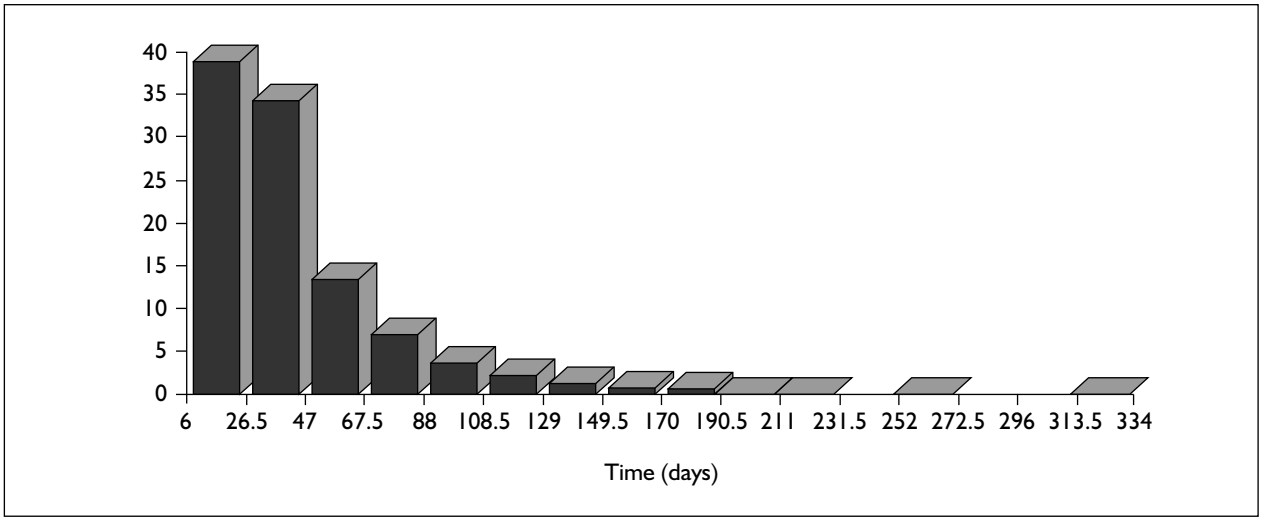


FIGURE 62 *Time to return a baseline questionnaire(all baseline responder,* n = *1587)*

who completed both baseline and 2-year follow-up questionnaires and so are the focus of the QoL analyses presented in this report, only 496 (48%) returned a baseline questionnaire within 30 days of randomisation, with a further 402 returning one between 30 and 60 days of randomisation [total of 898 (86%) returned within 60 days] (*Figure 63*). Of these 1042, 363 people had a seizure between the dates of randomisation and of return of their baseline questionnaires, and 58 people were withdrawn from the drug to which they were randomised between the dates of randomisation and of return of their baseline questionnaires. Thus, for a proportion of patients there was contamination of the baseline QoL assessment because of an intervening important clinical event.

With regard to follow-up questionnaires, including the 2-year follow-up, we have taken the view that a wider interval for return is acceptable. Of the 1042 participants under consideration here, 929 (89%) returned the 2-year questionnaire within 100 days of the 2-year time point since randomisation, and 1031 (99%) returned one within 6 months of the 2-year time point (*Figure 64*). Overall, 476 (46%) of the 1042 responded within 30 days at baseline and within 100 days at 2 years; 495 (48%) responded within 30 days at baseline and 6 months at 2 years; 832 (80%) responded within 60 days at baseline and 100 days at 2 years; and 890 (85%) responded within 60 days at baseline and 6 months at 2 years.

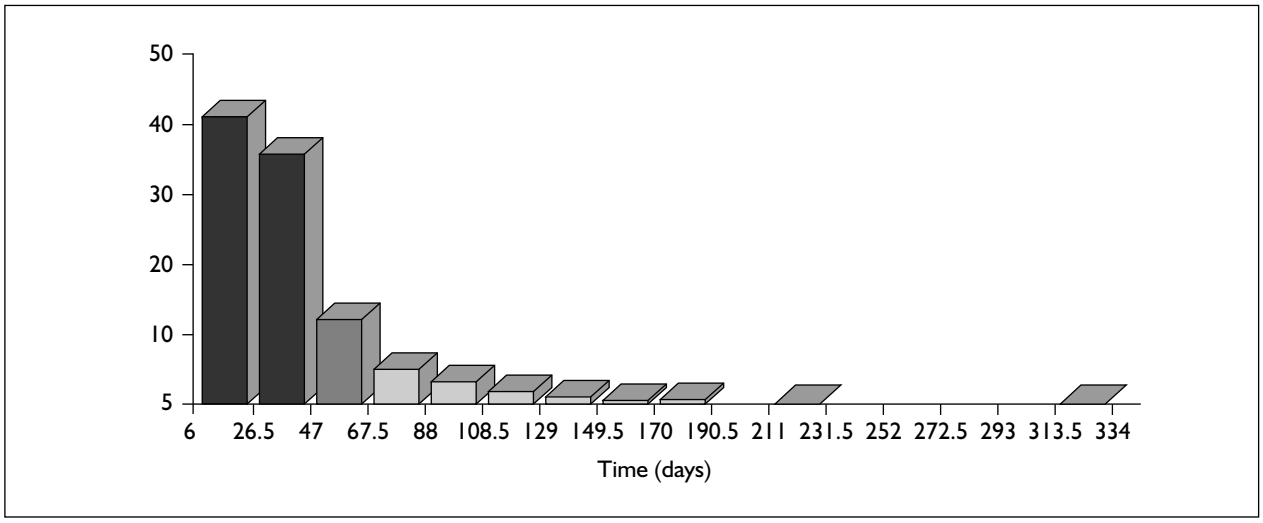


FIGURE 63 *Time to return a baseline questionnaire (2-year responders only,* n = *1042)*

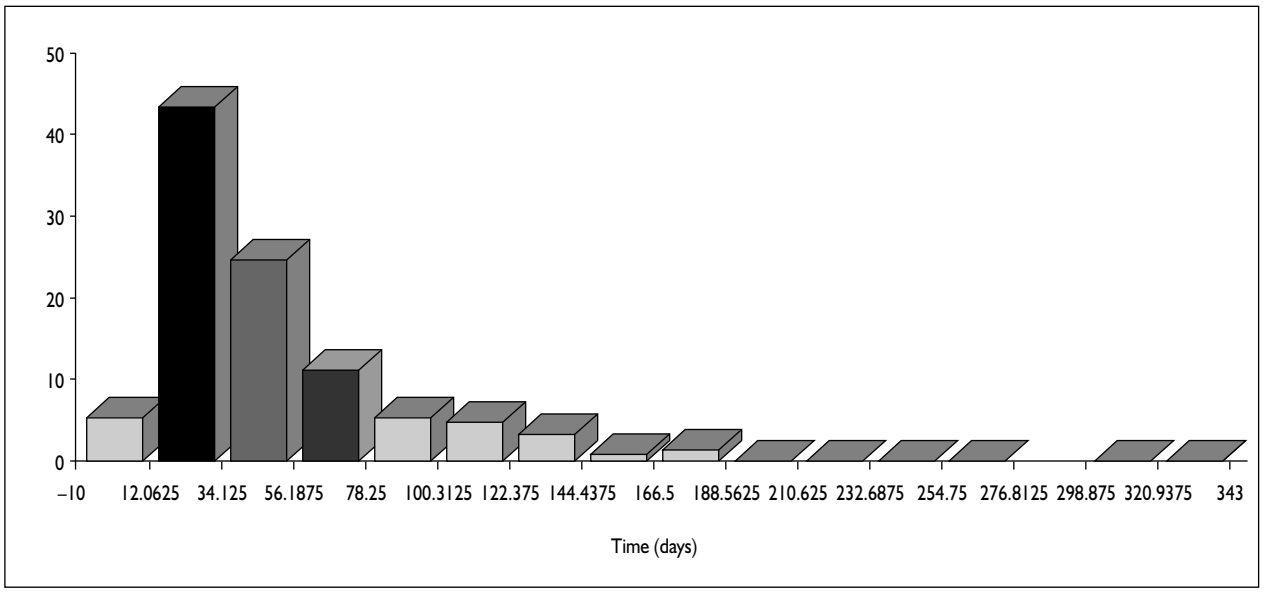


FIGURE 64 *Time to return a 2-year questionnaire* (n = *1042)*

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Feedback

The HTA Programme and the authors would like to know your views about this report.

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We look forward to hearing from you.

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