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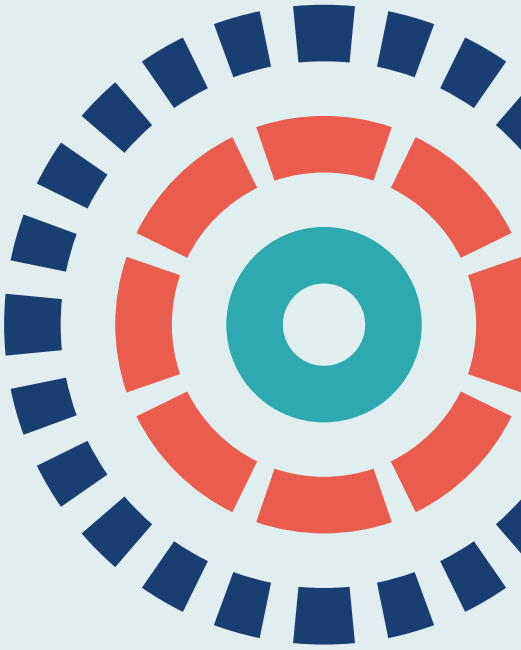

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Lamotrigine versus levetiracetam or zonisamide for focal epilepsy and valproate versus levetiracetam for generalised and unclassified epilepsy: two SANAD II non-inferiority RCTs

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for Health and Care Excellence Guidelines Group for Epilepsy (2019–21). Rajiv Mohanraj reports personal fees from UCB, and grants from UCB and Sanofi SA (Paris, France) outside the submitted work. Catrin Tudur-Smith reports a committee membership (HTA Commissioning Committee) (2015–20). Paula R Williamson was Director of Liverpool Clinical Trials Centre (formerly Medicines for Children Clinical Trials Unit) (April 2005–December 2018), which received funding from NIHR (end date 31 August 2021). She also reports grants from the University of Liverpool and from the NIHR HTA programme during the conduct of the study.

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Abstract

Lamotrigine versus levetiracetam or zonisamide for focal epilepsy and valproate versus levetiracetam for generalised and unclassified epilepsy: two SANAD II non-inferiority RCTs

Anthony G Marson,[1*] Girvan Burnside,[2] Richard Appleton,[3] Dave Smith,[4] John Paul Leach,[5] Graeme Sills,[1] Catrin Tudur-Smith,[2] Catrin O Plumpton,[6] Dyfrig A Hughes,[6] Paula R Williamson,[2] Gus Baker,[1] Silviya Balabanova,[7] Claire Taylor,[7] Richard Brown,[8] Dan Hindley,[9] Stephen Howell,[10] Melissa Maguire,[11] Rajiv Mohanraj[12] and Philip EM Smith[13] on behalf of the SANAD II collaborators

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Background: Levetiracetam (Keppra®, UCB Pharma Ltd, Slough, UK) and zonisamide (Zonegran®, Eisai Co. Ltd, Tokyo, Japan) are licensed as monotherapy for focal epilepsy, and levetiracetam is increasingly used as a first-line treatment for generalised epilepsy, particularly for women of childbearing age. However, there is uncertainty as to whether or not they should be recommended as first-line treatments owing to a lack of evidence of clinical effectiveness and cost-effectiveness.

Objectives: To compare the clinical effectiveness and cost-effectiveness of lamotrigine (Lamictal®, GlaxoSmithKline plc, Brentford, UK) (standard treatment) with levetiracetam and zonisamide (new treatments) for focal epilepsy, and to compare valproate (Epilim®, Sanofi SA, Paris, France) (standard treatment) with levetiracetam (new treatment) for generalised and unclassified epilepsy.

Design: Two pragmatic randomised unblinded non-inferiority trials run in parallel.

Setting: Outpatient services in NHS hospitals throughout the UK.

Participants: Those aged ≥ 5 years with two or more spontaneous seizures that require anti-seizure medication.

Interventions: Participants with focal epilepsy were randomised to receive lamotrigine, levetiracetam or zonisamide. Participants with generalised or unclassifiable epilepsy were randomised to receive valproate or levetiracetam. The randomisation method was minimisation using a web-based program.

Main outcome measures: The primary outcome was time to 12-month remission from seizures. For this outcome, and all other time-to-event outcomes, we report hazard ratios for the standard treatment compared with the new treatment. For the focal epilepsy trial, the non-inferiority limit (lamotrigine vs. new treatments) was 1.329. For the generalised and unclassified epilepsy trial, the non-inferiority limit (valproate vs. new treatments) was 1.314. Secondary outcomes included time to treatment failure, time to first seizure, time to 24-month remission, adverse reactions, quality of life and cost-effectiveness.

Results: *Focal epilepsy*. A total of 990 participants were recruited, of whom 330 were randomised to receive lamotrigine, 332 were randomised to receive levetiracetam and 328 were randomised to receive zonisamide. Levetiracetam did not meet the criteria for non-inferiority (hazard ratio 1.329) in the primary intention-to-treat analysis of time to 12-month remission (hazard ratio vs. lamotrigine 1.18, 97.5% confidence interval 0.95 to 1.47), but zonisamide did meet the criteria (hazard ratio vs. lamotrigine 1.03, 97.5% confidence interval 0.83 to 1.28). In the per-protocol analysis, lamotrigine was superior to both levetiracetam (hazard ratio 1.32, 95% confidence interval 1.05 to 1.66) and zonisamide (hazard ratio 1.37, 95% confidence interval 1.08 to 1.73). For time to treatment failure, lamotrigine was superior to levetiracetam (hazard ratio 0.60, 95% confidence interval 0.46 to 0.77) and zonisamide (hazard ratio 0.46, 95% confidence interval 0.36 to 0.60). Adverse reactions were reported by 33% of participants starting lamotrigine, 44% starting levetiracetam and 45% starting zonisamide. In the economic analysis, both levetiracetam and zonisamide were more costly and less effective than lamotrigine and were therefore dominated. *Generalised and unclassifiable epilepsy*. Of 520 patients recruited, 260 were randomised to receive valproate and 260 were randomised to receive to levetiracetam. A total of 397 patients had generalised epilepsy and 123 had unclassified epilepsy. Levetiracetam did not meet the criteria for non-inferiority in the primary intention-to-treat analysis of time to 12-month remission (hazard ratio 1.19, 95% confidence interval 0.96 to 1.47; non-inferiority margin 1.314). In the per-protocol analysis of time to 12-month remission, valproate was superior to levetiracetam (hazard ratio 1.68, 95% confidence interval 1.30 to 2.15). Valproate was superior to levetiracetam for time to treatment failure (hazard ratio 0.65, 95% confidence interval 0.50 to 0.83). Adverse reactions were reported by 37.4% of participants receiving valproate and 41.5% of those receiving levetiracetam. Levetiracetam was both more costly (incremental cost of £104, 95% central range –£587 to £1234) and less effective (incremental quality-adjusted life-year of –0.035, 95% central range –0.137 to 0.032) than valproate, and was therefore dominated. At a cost-effectiveness threshold of £20,000 per quality-adjusted life-year, levetiracetam was associated with a probability of 0.17 of being cost-effective.

Limitations: The SANAD II trial was unblinded, which could have biased results by influencing decisions about dosing, treatment failure and the attribution of adverse reactions.

Future work: SANAD II data could now be included in an individual participant meta-analysis of similar trials, and future similar trials are required to assess the clinical effectiveness and cost-effectiveness of other new treatments, including lacosamide and perampanel.

Conclusions: *Focal epilepsy* – The SANAD II findings do not support the use of levetiracetam or zonisamide as first-line treatments in focal epilepsy. *Generalised and unclassifiable epilepsy* – The SANAD II findings do not support the use of levetiracetam as a first-line treatment for newly diagnosed generalised epilepsy. For women of childbearing potential, these results inform discussions about the benefit (lower teratogenicity) and harm (worse seizure outcomes and higher treatment failure rate) of levetiracetam compared with valproate.

Trial registration: Current Controlled Trials ISRCTN30294119 and EudraCT 2012-001884-64.

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Contents

List of tables

List of figures

List of abbreviations

A&E	accident and emergency
AE	adverse event
AR	adverse reaction
AUC	area under the curve
CC	complication and comorbidity
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CR	central range
CRF	case report form
CSRI	Client Service Receipt Inventory
CT	computerised tomography
DNA	deoxyribonucleic acid
EEG	electroencephalography
EMA	European Medicines Agency
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
EQ-5D-3L-Y	EuroQol-5 Dimensions, three-level version (youth version)
GP	general practitioner
HES	Hospital Episode Statistics
HR	hazard ratio
HRG	Health Resource Group
ICER	incremental cost-effectiveness ratio
IDSMC	Independent Data and Safety Monitoring Committee
INHB	incremental net health benefit
IQR	interquartile range
ISC	inadequate seizure control
ITT	intention to treat
LCTC	Liverpool Clinical Trials Centre
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
NEWQOL	Quality of Life in Newly Diagnosed Epilepsy Instrument
NHB	net health benefit
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
PP	per protocol
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
SAR	serious adverse reaction
SD	standard deviation
SUSAR	suspected unexpected serious adverse reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	unacceptable adverse reaction
VAS	visual analogue scale

Plain English summary

Background and methods

The SANAD II trial was a clinical trial designed to identify the most clinically effective and cost-effective treatment for adults and children aged > 5 years with newly diagnosed epilepsy.

There are two main epilepsy types: focal and generalised. In focal epilepsy, seizures start at a single place in the brain (a focus), whereas in generalised epilepsy seizures start in both sides of the brain at the same time.

Anti-seizure medications are the main treatment. For people with newly diagnosed epilepsy, the first anti-seizure medication should control the seizures as quickly as possible while avoiding side effects. The first-choice treatments are lamotrigine (Lamictal®, GlaxoSmithKline plc, Brentford, UK) for focal epilepsy and valproate (Epilim®, Sanofi SA, Paris, France) for generalised epilepsy (however, the latter should be avoided in women who could become pregnant).

A number of newer anti-seizure medications have been approved for NHS use, but it is unclear whether or not they should be used as first-line treatments. The SANAD II trial focused on the new medicines levetiracetam (Keppra®, UCB Pharma Ltd, Slough, UK) and zonisamide (Zonegran®, Eisai Co. Ltd, Tokyo, Japan).

We recruited 1510 people aged ≥ 5 years with newly diagnosed epilepsy: 990 with focal epilepsy and 520 with generalised or unclassified epilepsy.

Findings: focal epilepsy

People starting treatment with levetiracetam or zonisamide were significantly less likely to have a 12-month remission from seizures than people starting treatment with lamotrigine, unless they were changed to another anti-seizure medication. Side effects that were thought to be caused by anti-seizure medications were reported by 33% of participants starting lamotrigine, 44% of those starting levetiracetam and 45% of those starting zonisamide.

The cost-effectiveness analyses showed that neither levetiracetam nor zonisamide is value for money for the NHS when compared with lamotrigine.

The SANAD II findings do not support the use of levetiracetam or zonisamide as first-line treatments in focal epilepsy.

Findings: generalised and unclassifiable epilepsy

People starting treatment with levetiracetam were significantly less likely to have a 12-month remission from seizures than people starting valproate, unless they were changed to another anti-seizure medication. Side effects that were thought to be caused by anti-seizure medications were reported by 37% of participants starting valproate and 42% of participants starting levetiracetam.

The cost-effectiveness analyses showed that levetiracetam is not good value for money for the NHS when compared with valproate.

The SANAD II findings do not support the use of levetiracetam as a first-line treatment for newly diagnosed generalised epilepsy. Importantly, our results will inform treatment decisions for women, who may choose a less effective treatment that is safer in pregnancy.

Scientific summary

Background

Levetiracetam (Keppra®, UCB Pharma Ltd, Slough, UK) and zonisamide (Zonegran®, Eisai Co. Ltd, Tokyo, Japan) are licensed for use as monotherapy in focal epilepsy, but there is uncertainty as to whether or not they should be recommended as first-line treatments because of the lack of evidence from randomised trials regarding their longer-term clinical effectiveness and cost-effectiveness.

There is also uncertainty about the clinical effectiveness and cost-effectiveness of levetiracetam for generalised and unclassified epilepsy. This is particularly important for those with newly diagnosed idiopathic generalised epilepsy, for whom valproate (Epilim®, Sanofi SA, Paris, France) is a recommended first-line treatment for men but not women of childbearing potential because it is teratogenic. Despite inadequate evidence, levetiracetam is increasingly prescribed as an alternative to valproate.

The SANAD II trial assessed the longer-term clinical effectiveness and cost-effectiveness of levetiracetam and zonisamide compared with the standard treatment lamotrigine (Lamictal®, GlaxoSmithKline plc, Brentford, UK) for focal epilepsy, and of levetiracetam compared with the standard treatment valproate for generalised and unclassifiable epilepsy.

Methods

The SANAD II trial comprised two randomised unblinded controlled trials running in parallel. One compared the policies of starting treatment with levetiracetam, zonisamide or lamotrigine for focal epilepsy. The second compared the policies of starting treatment with levetiracetam or valproate for generalised or unclassified epilepsy. Adult and paediatric neurology services across the UK recruited participants aged ≥ 5 years who had experienced two or more unprovoked seizures requiring treatment.

The primary outcome was time to 12-month remission. The SANAD II trial was designed to assess the non-inferiority of both levetiracetam and/or zonisamide compared with lamotrigine. The non-inferiority limit was an absolute difference of 10%, which equates to a hazard ratio (HR) of 1.329. The SANAD II trial was also designed to assess the non-inferiority of levetiracetam compared with valproate. The non-inferiority limit was an absolute difference of 10%, which equates to a HR of 1.314.

Secondary outcomes were times to treatment failure overall and for inadequate seizure control (ISC) or unacceptable adverse reactions (UAR) individually, time to first seizure, time to 24-month remission, adverse effects and quality of life. Cost-effectiveness was from the perspective of the NHS and Personal Social Services in the UK, and based on the incremental costs per quality-adjusted life-year (QALY) gained. A HR > 1 indicates that an event is more likely on the standard treatment (lamotrigine or valproate) in each trial.

Results

Focal epilepsy

A total of 990 participants were recruited between April 2013 and June 2017, and were followed up for a further 2 years. The mean age was 39.3 years (range 5.0–91.9 years), 56.7% were male, and the median number of seizures was 6 (interquartile range 3–24). Levetiracetam did not meet the criteria

for non-inferiority (HR 1.329) in the primary intention-to-treat (ITT) analysis of time to 12-month remission [HR vs. lamotrigine 1.18, 97.5% confidence interval (CI) 0.95 to 1.47], but zonisamide did meet the criteria (HR vs. lamotrigine 1.03, 97.5% CI 0.83 to 1.28). The per-protocol (PP) analysis found superiority of lamotrigine over both levetiracetam (HR 1.32, 97.5% CI 1.05 to 1.66) and zonisamide (HR 1.37, 95% CI 1.08 to 1.73). For time to treatment failure (any reason), lamotrigine was superior to levetiracetam (HR 0.60, 95% CI 0.46 to 0.77) and zonisamide (HR 0.46, 95% CI 0.36 to 0.60).

Treatment failure due to adverse reactions (ARs) was significantly more likely with levetiracetam (HR 0.53, 95% CI 0.35 to 0.79) and zonisamide (HR 0.37, 95% CI 0.25 to 0.55) than with lamotrigine. Although not statistically significant, estimates indicated that treatment failure due to inadequate seizure control was more likely with levetiracetam (HR 0.67, 95% CI 0.45 to 1.01) and zonisamide (HR 0.76, 95% CI 0.50 to 1.15) than with lamotrigine. ARs were reported by 33% of participants starting lamotrigine, 44% starting levetiracetam and 45% starting zonisamide.

In the economic analysis, levetiracetam was associated with a QALY gain of 1.474 years [97.5% central range (CR) 1.393 to 1.523 years], zonisamide with a QALY gain of 1.502 years (97.5% CR 1.418 to 1.566 years), and lamotrigine with a QALY gain of 1.605 years (97.5% CR 1.547 to 1.651 years). The mean total cost was £5104 (97.5% CR £4450 to £6141) for levetiracetam, £5400 (97.5% CR £4659 to £6770) for zonisamide, and £4042 (97.5% CR £3626 to £4983) for lamotrigine. Both levetiracetam and zonisamide were therefore dominated by lamotrigine.

Generalised and unclassifiable epilepsy

A total of 520 participants were recruited between April 2013 and August 2016, and were followed up for a further 2 years. The mean age was 17.0 years (range 5.0–94.4 years), 64.8% were male, 397 participants had generalised epilepsy and 123 had unclassified epilepsy. Levetiracetam did not meet the criteria for non-inferiority in the primary ITT analysis of time to 12-month remission (HR 1.19, 95% CI 0.96 to 1.47; non-inferiority margin 1.314). There was evidence of a non-constant HR over time ($p < 0.01$), and time-to-event probabilities indicate an initial difference that diminished over time. The immediate 12-month remission rate was 26% for those starting levetiracetam and 36% for those starting valproate (difference 9%, 95% CI 1% to 18%). At 3 years, these rates were 74% for those starting levetiracetam and 73% for those starting valproate. The PP analysis of time to 12-month remission found superiority of valproate over levetiracetam (HR 1.68, 95% CI 1.30 to 2.15). Valproate was also superior to levetiracetam for time to 24-month remission (HR 1.43, 95% CI 1.06 to 1.92) and time to first seizure (HR 0.82, 95% CI 0.67 to 1.00).

Valproate was superior to levetiracetam for time to treatment failure (HR 0.65, 95% CI 0.50 to 0.83) and for treatment failure due to ISC (HR 0.43, 95% CI 0.30 to 0.63); treatment failure rates due to UAR were similar (HR 0.93, 95% CI 0.61 to 1.40). AR rates were similar, but profiles differed: there were 220 ARs in 96 (37.4%) participants randomised to receive valproate and 223 ARs in 107 (41.5%) participants randomised to receive levetiracetam. There were psychiatric symptoms in 66 of those randomised to receive levetiracetam and in 36 of those randomised to receive valproate. Eight participants randomised to receive levetiracetam had gained weight, compared with 26 participants who were randomised to receive valproate.

The economic analysis indicated levetiracetam to be associated with a QALY gain of 1.603 years (95% CR 1.500 to 1.631 years) compared with 1.637 years (95% CR 1.565 to 1.673 years) for valproate. The mean total cost was £4350 (95% CR £4136 to £5623) for levetiracetam and £4246 (95% CR £3979 to £5090) for valproate. Levetiracetam was, therefore, dominated by valproate. Levetiracetam is associated with a negative incremental net health benefit (–0.040 95% CR –0.175 to 0.037) at a cost-effectiveness threshold of £20,000 per QALY.

Conclusions

Focal epilepsy

The SANAD II findings do not support the use of levetiracetam or zonisamide as first-line treatments in focal epilepsy. Although zonisamide met the criteria for non-inferiority in the ITT 12-month remission analysis, levetiracetam did not. The PP analysis accounting for treatment failure found both levetiracetam and zonisamide to be inferior to lamotrigine. Levetiracetam and zonisamide were significantly more likely to fail, were associated with more ARs, and did not meet the criteria for cost-effectiveness operating in the NHS.

Generalised and unclassifiable epilepsy

The SANAD II findings do not support the use of levetiracetam as a first-line treatment for newly diagnosed generalised epilepsy. For women of childbearing potential, these results inform discussions about benefit (lower teratogenicity) and harm (worse seizure outcomes and higher treatment failure rate) of levetiracetam compared with valproate.

Trial registration

This trial is registered as ISRCTN30294119 and EudraCT 2012-001884-64.

Funding

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Chapter 1 Introduction

Epilepsy is a common condition, with a prevalence of 0.5–1% and a lifetime incidence of up to 5%.[1] It is also a complex condition with many different causes and a number of seizure types and syndromes, as defined by the International Leagues Against Epilepsy.[2,3] It is uniquely stigmatising and has a negative impact on quality of life (QoL), education and employment prospects.[4,5] Anti-seizure medicines, previously called antiepileptic drugs, are the mainstay of treatment and may need to be a lifelong treatment. The aim of treatment is to maximise QoL by eliminating seizures at drug doses that do not cause adverse effects. The choice of first anti-seizure medicine is paramount if we are to maximise individuals' educational and career prospects, their ability to return to work and their ability to drive.

Around two-thirds of people with epilepsy have focal epilepsy, in which seizures originate within networks limited to one cerebral hemisphere. Seizure types include focal aware seizures (previously called simple partial seizures), focal seizures with altered awareness (previously called complex partial seizures) and focal to bilateral tonic–clonic seizures (previously called secondary generalised tonic–clonic seizures).[2,3] Focal epilepsy can start at any age, and the incidence distribution is U-shaped, with a higher incidence in the young and the elderly. Owing to the ageing population in many countries, the incidence is higher in the elderly than in the young.[6]

Although focal epilepsies can be classified according to the site of seizure onset and aetiology, there is no evidence to suggest that one syndrome or aetiology responds better to one treatment than to another.[7] Drug management is therefore generally similar whatever the aetiology or syndrome. Guidelines typically recommend lamotrigine (Lamictal®, GlaxoSmithKline plc, Brentford, UK) or carbamazepine (Tegretol®, Novartis Pharmaceuticals UK Ltd, London, UK) as first-line treatments,[8] in part informed by the first SANAD trial, which identified lamotrigine as non-inferior to carbamazepine for time to 12-month remission and superior to carbamazepine, gabapentin (Neurontin®, Upjohn UK Ltd, Sandwich, UK), oxcarbazepine (Trileptal®, Novartis Pharmaceuticals UK Ltd) and topiramate (Topamax®, Janssen: Pharmaceutical Companies of Johnson & Johnson, Beerse, Belgium) for time to treatment failure.[9] Lamotrigine was therefore chosen as the standard comparator in the SANAD II trial.

Around one-third of people with epilepsy have idiopathic generalised epilepsy, also referred to as genetic generalised epilepsy, which includes several syndromes classified according to seizure type and age at onset, such as the absence epilepsies and juvenile myoclonic epilepsy.[3] Although the differing syndromes are recognised, there is currently no reliable evidence that relative treatment responses differ across syndromes. Indeed, prognostic modelling of data from the SANAD I trial indicates that relative treatment responses are consistent across syndromes.[7] In addition, at the time of epilepsy diagnosis, classification can be difficult for a proportion of people who cannot be classified as having either a focal or a generalised epilepsy, although for many a syndromic diagnosis can be made during follow-up as investigation results are received or more seizures are observed.[10,11]

For many years, despite limited evidence from randomised controlled trials (RCTs), valproate (Epilim®, Sanofi SA, Paris, France) has been recommended as a first-line treatment for generalised and unclassifiable epilepsy as it has a broad spectrum of action.[12] Cochrane reviews have compared valproate with other anti-seizure medicines,[13–15] but, because of problems with power and epilepsy classification, they have not shown an advantage for valproate. The SANAD I trial identified valproate as a clinically effective and cost-effective alternative to either lamotrigine or topiramate,[16] and a double-blind trial of 16 weeks' therapy in childhood and juvenile absence epilepsy found that both valproate and ethosuximide were superior to lamotrigine for the outcome time to treatment failure.[17]

Valproate is not recommended for women of childbearing potential, as it is associated with a major malformation rate of around 10%,[15] and up to one-third of children exposed in utero have a significant reduction in their IQ.[16] In 2017, the European Medicines Agency (EMA) and the UK Medicines and

Healthcare products Regulatory Agency (MHRA) launched a pregnancy prevention programme,[18] stating that women should not be prescribed valproate unless other treatments are ineffective or not tolerated. Consequently, making a treatment choice for women with idiopathic generalised epilepsy is very challenging. The two main alternatives to valproate are lamotrigine, which is less effective but safer in pregnancy, and levetiracetam (Keppra®, UCB Pharma Ltd, Slough, UK), for which we have increasing evidence of relative safety in pregnancy,[19,20] but its effectiveness compared with valproate is unknown.

Although > 20 anti-seizure medicines have been licensed for use globally in the past 20 years, there is very limited evidence to inform everyday decisions, including choice of first anti-seizure medicine, because regulatory trials do not measure important longer-term outcomes (e.g. 12-month remission from seizures). In particular, very few trials have assessed the comparative clinical effectiveness or cost-effectiveness of anti-seizure medications for generalised epilepsy or epilepsy that is difficult to classify.[12] The SANAD collaborators selected levetiracetam and zonisamide (Zonegran®, Eisai Co. Ltd, Tokyo, Japan) for assessment in the SANAD II trial.

Levetiracetam is a commonly prescribed anti-seizure medication with evidence of efficacy as monotherapy in focal epilepsy. This is based on finding non-inferiority when comparing levetiracetam with carbamazepine for 6-month seizure remission, and finding similar tolerability of both medications in a regulatory trial that did not assess longer-term effectiveness.[21] A second unblinded trial compared levetiracetam with the physician's choice of carbamazepine or valproate[22] and found no significant difference between carbamazepine and levetiracetam for time to first seizure and time to treatment failure. However, this trial[22] had a maximum follow-up of 12 months and could not assess the longer-term outcomes needed to inform policy. In the 2012 National Institute for Health and Care Excellence (NICE) epilepsy guideline,[8] levetiracetam was not recommended as a first-line treatment based on an analysis indicating that it was not cost-effective; however, it has since become widely prescribed. Generic levetiracetam has been available in the UK since 2011, and the price of 60 × 250-mg tablets (for example) has since reduced from £29.70[23] to £5.72.[24]

Levetiracetam has been increasingly used as a first-line treatment in generalised epilepsy,[25] particularly for women of childbearing age. Although there is RCT evidence of efficacy as an add-on treatment for some generalised seizure types,[26,27] and evidence of tolerability as monotherapy when compared with valproate,[22] there is currently no RCT evidence of clinical effectiveness, cost-effectiveness or economic evidence supporting the cost-effectiveness of levetiracetam when used as monotherapy or as a first-line treatment in generalised or unclassifiable epilepsy.

Zonisamide has been available for many years in Japan[28] and other countries in South-East Asia, where it is commonly used both as initial monotherapy and as an add-on treatment. Its licence for use as monotherapy in focal epilepsy is based on a regulatory study demonstrating non-inferiority when compared with carbamazepine for 6-month seizure remission rates.[29] The longer-term comparative clinical effectiveness and cost-effectiveness of zonisamide in focal epilepsy are unknown, and zonisamide is not currently recommended as a first-line therapy. Zonisamide currently costs more than 12 times as much as lamotrigine on a defined daily dose basis.

The aims of the SANAD II trial were to assess the longer-term clinical effectiveness and cost-effectiveness of levetiracetam and zonisamide compared with lamotrigine in focal epilepsy, and of levetiracetam compared with valproate for generalised or unclassifiable epilepsy, in an unblinded randomised controlled trial.

Chapter 2 Trial design and methods

Study design

The SANAD II trial was a pragmatic Phase IV, multicentre, unblinded randomised controlled trial that was conducted in NHS adult neurology and paediatric services. The study was essentially two separate RCTs: the first trial recruited participants with newly diagnosed focal epilepsy who were randomised to start treatment with the 'standard' drug lamotrigine or with the 'new' drugs levetiracetam or zonisamide, and the second trial recruited participants with newly diagnosed generalised epilepsy or epilepsy that was unclassified at the time of randomisation, who were randomised to start treatment with the 'standard' drug valproate or with the 'new' drug levetiracetam. Both trials followed the previously published protocol.[30] An economic evaluation was performed to consider the cost-effectiveness of newer drugs compared with the standard drugs. A schematic of the study design is provided in *Figure 1*.

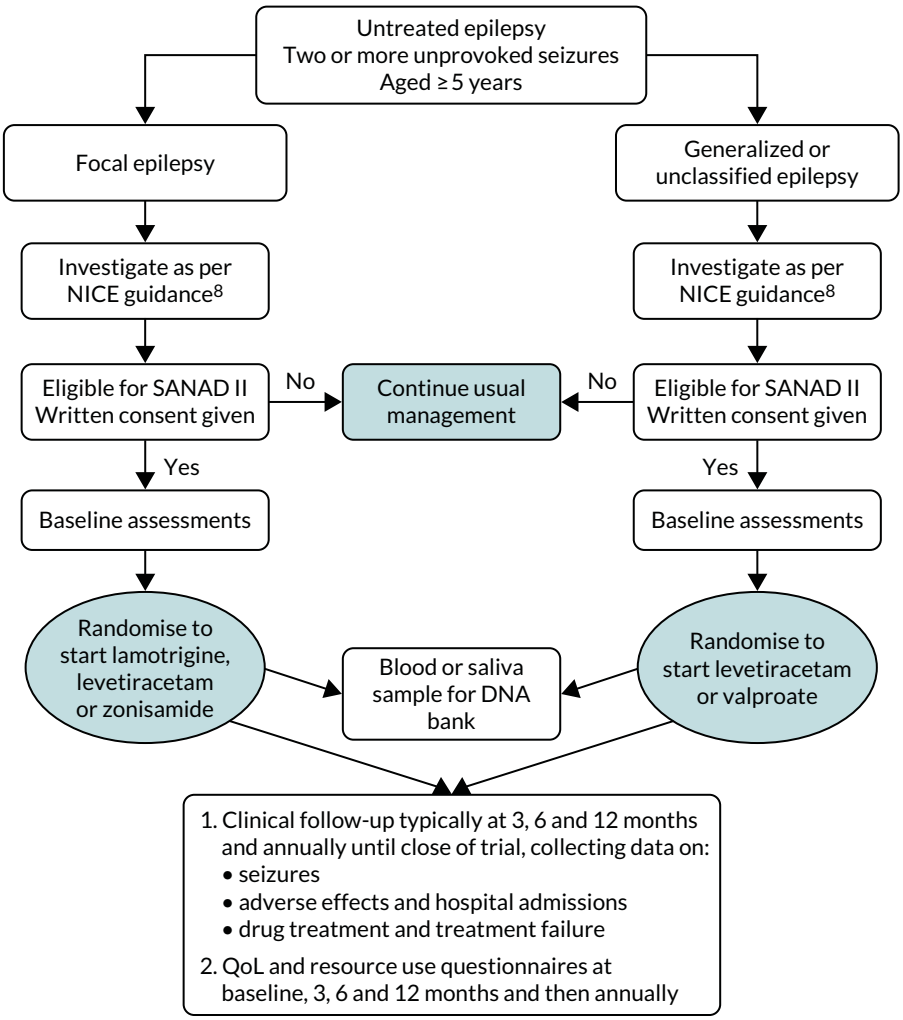

FIGURE 1 Schematic of study design.

Study sites

Participants were recruited from NHS outpatient epilepsy, general neurology and paediatric (epilepsy and general) clinics in the UK. The study was co-ordinated through the UK Epilepsy Research Network, the Medicines for Children Research Network, the Wales Epilepsy Research Network and the Comprehensive Clinical Research Network. To be eligible to participate in the study, staff at the sites had to be experienced in treating epilepsy.

Participants

We aimed to recruit 1510 patients (990 with focal onset seizures and 520 with generalised onset seizures or difficult to classify seizures) with the following characteristics.

Inclusion criteria

- Aged $\geq$ 5 years.
- Previously experienced two or more spontaneous seizures that required anti-seizure medication.
- Untreated and not previously treated with anti-seizure medication, except as emergency treatment, in the past 2 weeks.
- Anti-seizure medication monotherapy considered the most appropriate option.
- Willing to provide consent (patient's parent/legal representative willing to give consent where the patient is aged < 16 years or is lacking capacity to consent).

Exclusion criteria

- Provoked seizures only (e.g. alcohol or drug induced).
- Acute symptomatic seizures only (e.g. within 1 month of acute brain haemorrhage, brain injury or stroke).
- Currently treated with anti-seizure medication.
- Progressive neurological disease (e.g. known brain tumour).

Recruitment procedure

Patients aged $\geq$ 5 years who had had two or more spontaneous seizures that required anti-seizure medication and had not previously been treated with anti-seizure medication were screened at the study centre sites to identify participants potentially eligible for the study. Potentially eligible patients (i.e. those meeting the eligibility criteria listed), or their parent/legally acceptable representative, where appropriate, were invited to participate in the study and were provided with a patient information sheet and consent form. The patient (or their parent/legally acceptable representative) was allowed sufficient time to discuss the trial and to decide whether or not to consent to trial entry.

Informed consent

Informed, written consent to enter the SANAD II study was obtained at the baseline visit. The original copy of the signed and dated consent form was filed in the participant's notes. One copy of the signed consent form was given to the patient (or their parent or legal representative in the case of minors and adults with incapacity) for their records, one copy was retained in the investigator site file, and a final copy was sent to the co-ordinating centre.

If capable, and under appropriate circumstances, minors were approached to provide assent by a member of the research team with experience working with minors. The absence of assent did not exclude the patient, provided that consent had been obtained from the parent/legal representative.

For adults lacking capacity, trial participation was discussed with a personal (or professional) legal representative by a suitably experienced member of the research team. For England, Wales and Northern Ireland, a personal legal representative is someone suitable by virtue of their relationship with the adult and who is available and willing to be the personal legal representative. For Scottish sites, a personal legal representative is a welfare guardian, welfare attorney or nearest relative. They were provided with written information and asked to sign the patient representative consent form.

Informed consent for deoxyribonucleic acid collection

Deoxyribonucleic acid (DNA) collection was included as an additional option in the main SANAD II informed consent form, and the same process for obtaining informed consent was followed to obtain consent. Refusal for DNA collection did not preclude participation in the main SANAD II trial. Analysis of DNA will be funded by future applications.

Randomisation, concealment and blinding

Once eligibility criteria had been confirmed and informed consent and assent, when appropriate, had been obtained, the recruiting clinician selected the appropriate trial based on the patient's epilepsy classification (focal vs. generalised or unclassified). Patients with focal epilepsy were then randomised in a 1 : 1 : 1 ratio to lamotrigine, levetiracetam or zonisamide; patients with generalised and unclassifiable epilepsy were randomised in a 1 : 1 ratio to levetiracetam or valproate.

Randomisation was performed using a secure (24-hour) web-based randomisation program that was controlled centrally by the Liverpool Clinical Trials Centre (LCTC). A personal login (username and password), provided by the LCTC, was required to access the randomisation system.

Patients were allocated a unique study number (randomisation number) and treatment allocation, displayed to the authorised randomiser on a secure web page, and an automated e-mail confirmation was sent to the authorised randomiser, principal investigator and the trial co-ordinator.

Randomisation used a minimisation program with a built-in random element utilising factors for centre, sex (male or female) and number of previous seizures (two, three to five, or six or more). The factors used for minimisation were not made known to the recruiting sites to avoid any risk of them predicting allocation. The recruiting clinicians were required to initiate trial treatment within 7 days of randomisation.

The SANAD II trial was unblinded, trial treatments were prescribed as per routine NHS practice and dispensed by hospital and community pharmacies, and clinicians prescribed the formulation they considered most appropriate.

Treatment group allocation

The aim of treatment was to control seizures with the minimum effective dose of drug. The trial protocol[30] provided guidance on initial drug titration and maintenance doses based on the routine practice at the time that the trial was initiated, although clinicians were able to tailor this as they considered appropriate.

Focal epilepsy

For participants aged ≥ 12 years, the initial advised maintenance doses were 50 mg of lamotrigine in the morning and 100 mg in evening, 500 mg of levetiracetam twice per day or 100 mg of zonisamide twice per day. For children aged 5–12 years, the initial daily maintenance doses advised were 1.5 mg/kg lamotrigine twice per day, 40 mg/kg levetiracetam twice per day in two divided doses or 2.5 mg/kg zonisamide twice per day. The subsequent dose and treatment changes at follow-up visits were made in accordance with routine clinical practice, depending on the treatment response and adverse effects.

Generalised or unclassified epilepsy

For participants aged ≥ 12 years, the initial advised maintenance doses were 500 mg twice per day for both levetiracetam or valproate. For children aged 5–12 years, the initial daily maintenance doses advised were 25 mg/kg valproate or 40 mg/kg levetiracetam. The subsequent dose and treatment changes at follow-up visits were made in accordance with routine clinical practice, depending on the treatment response and adverse effects.

The decision to change or discontinue the allocated trial treatment was at the discretion of the treating physician and patient. Treatment could be changed or discontinued at any point during the trial period for reasons such as inadequate seizure control, unacceptable adverse events (AEs), or any change in the participant's condition that the physician believed warranted a change in medication. Any changes in medication were documented on the appropriate follow-up case report form (CRF), along with the justification for those changes, and patients were encouraged to continue to attend follow-up visits for the remainder of the study. At the end of the trial, participation patients were to continue their treatment as per local policy.

Data collection and management

The majority of clinical data were collected using paper CRFs that were completed by personnel (usually the research nurse) during clinic visits. The paper CRFs were photocopied for local records and originals were returned to the co-ordinating centre for data entry onto a MACRO 4 database (Macro 4 Ltd, Crawley, UK). Where patients defaulted from clinic follow-up, additional information was sought from general practitioners (GPs). Patients were asked to record data on seizures in patient seizure diaries, which were used as an aide-memoire at clinic follow-up visits.

Quality-of-life and utility assessments

Patients were asked to complete questionnaires so that QoL and resource use data could be collected. Questionnaires were either issued during clinic visits or posted to patients for completion at home, with the postal service used to return completed questionnaires. The LCTC contacted non-responders by telephone, typically 3 weeks following the issue of questionnaires.

For adults, QoL outcomes were assessed using subscales of the Quality of Life in Newly Diagnosed Epilepsy Instrument (NEWQOL) battery and the Impact of Epilepsy Scale.[31] For children and adolescents aged < 16 years, QoL assessment involved both patient- and parent-based measures: children aged 8–15 years completed a generic health status measure validated for use in epilepsy [the KINDL (generic quality-of-life instrument for children)],[32] as well as the 'epilepsy impact' and 'attitude to epilepsy' subscales of the QOLIE-AD (set of subscales for evaluation of health-related quality-of-life in adolescents with epilepsy).[33] Parents of all children completed proxy QoL questionnaires.

Utility scores were elicited directly from trial participants (or indirectly via parents/guardians). Adult and adolescent participants were asked to complete the EuroQol-5 Dimensions, three-level version (EQ-5D-3L), questionnaire and visual analogue scale (VAS). The EQ-5D-3L has been used previously in children, but it has not been formally validated,[34] and EQ-5D-3L weights are validated for adults aged ≥ 18 years. The currently recommended approach of using parental proxy reports of QoL for this age group was used.[35] The EQ-5D-3L-Y EuroQol-5 Dimensions, three-level version (youth version) (EQ-5D-3L-Y) was also administered to children aged 8–15 years. All trial participants were also asked to complete an epilepsy-specific utility

measure based on the NEWQOL-6D questionnaire.[36] QoL questionnaires were completed at baseline and annually thereafter. Adults and parents also completed a subset of QoL measures at 3 and 6 months.

Data on direct costs of health-care resources used by trial participants were collected via a modified version of the Client Service Receipt Inventory (CSRI)[37] that was included in the QoL questionnaires, access to Hospital Episode Statistics (HES) data, and recording of adverse reactions (ARs) requiring hospitalisation in follow-up CRFs. Unit costs were taken from the *NHS Reference Costs 2017/18*[38] database and other appropriate sources.[39,40]

Genetic substudy

DNA was to be collected from every patient randomised in the SANAD II trial, subject to appropriate consent.

Samples, preferably in the form of whole venous blood, were collected at baseline (or at a subsequent follow-up visit, as convenient), shipped to the Department of Molecular and Clinical Pharmacology at the University of Liverpool and DNA was extracted and stored in a state-of-the-art DNA archive. Saliva samples were collected from patients who were unable to provide a blood sample. This DNA, along with the DNA stored as part of the SANAD I trial, forms a unique cohort from whom we have collected DNA linked to prospective follow-up from diagnosis that will contribute to future studies of the genetic contributions to epilepsy and treatment response.

Baseline assessment

Following consent from the patient (or parent/legal representative), the delegated member of the research team completed the baseline CRF to collect data, including seizure history, history of neurological insult or febrile seizures, family history of epilepsy, and the results of electroencephalography (EEG) or imaging [computerised tomography (CT) or magnetic resonance imaging (MRI)]. If further investigations (EEG or imaging) were requested at this visit, data on the results were collected when available, but randomisation was not delayed. If a DNA sample was provided, then the DNA sample CRF was completed. Once all eligibility criteria had been assessed, full eligibility was confirmed by a doctor who had been authorised to do so on the site delegation log; a record of this confirmation was made in the patient's medical notes. Following the eligibility confirmation, the patient was then randomised.

Follow-up

The expected duration of follow-up for each participant was between 2 and 6.5 years, with visits planned as per routine practice: typically at 3, 6, and 12 months and annually thereafter. Patients could be seen at other times as clinically indicated. All patients were to be followed up even if allocated treatment had been withdrawn. We aimed to complete recruitment over a 4.5-year period, but a 12-month extension was required to meet the sample size target for the focal epilepsy trial, after which the trial cohort was followed up for a further 2 years, allowing a minimum follow-up of 2 years and maximum of 7.5 years for patients in the focal epilepsy trial.

Outcome measures

Primary outcome

The primary outcome was time to 12-month remission from seizures, calculated as days from randomisation to the first date at which a period of 12 months had elapsed without any seizures. For patients who did not experience a 12-month remission from seizures, observations were censored at the last follow-up visit.

Secondary outcomes

Time to 24-month remission

The time to 24-month remission from seizures was calculated as days from randomisation to the first date at which a period of 24 months had elapsed without any seizures. For patients who did not experience a 24-month remission from seizures, observations were censored at the last follow-up visit.

Time to first seizure

The time to first seizure was calculated as the number of days from randomisation to the first date at which a seizure (of any type) occurred. For patients who did not experience a seizure after randomisation, observations were censored at the last follow-up visit.

Treatment failure

Treatment failure is defined as withdrawal from randomised drug, or addition of a new anti-seizure medicine, where the reason is an unacceptable adverse reaction (UAR) or inadequate seizure control (ISC). Treatment failures, UARs and ISC are defined in *Table 1*, and treatment failure was measured using three outcomes:

1. Time to treatment failure overall was defined as the number of days from randomisation to a decision to withdraw the randomised drug or add a new anti-seizure medication because of ISC or a UAR. For patients who did not experience a failure due to either ISC or a UAR after randomisation, observations were censored at the last follow-up visit, or the date of treatment withdrawal, when applicable.
2. Time to treatment failure because of ISC was defined as the number of days from randomisation to a decision to withdraw the randomised drug or add a new anti-seizure medication because of ISC. For patients who did not experience a failure because of ISC after randomisation, observations were censored at the last follow-up visit, or the date of treatment withdrawal, where applicable.
3. Time to treatment failure because of UARs was defined as the number of days from randomisation to a decision to withdraw the randomised drug or add a new anti-seizure medication because of a UAR. For patients who did not experience a failure because of a UAR after randomisation, observations were censored at the last follow-up visit, or the date of treatment withdrawal, when applicable.

Adverse reactions

All ARs for which the causal relationship to the trial antiepileptic treatments was assessed and judged by the investigator to be possibly, probably or almost certainly related the antiepileptic treatment were recorded at each follow-up visit. These ARs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) (www.meddra.org/) dictionary to the most appropriate lower-level term, preferred term and the higher-level System Organ Classification by the trial staff at LCTC, with clinical oversight by the chief investigator.

Sample size

The SANAD II trial was powered to detect non-inferiority of the new anti-seizure medications (levetiracetam and zonisamide) compared with standard treatments [lamotrigine (for focal epilepsy) or valproate (for generalised or unclassified epilepsy)] for the primary outcome time to 12-month remission. A new drug might become a standard first-line treatment if it is proven to be non-inferior for efficacy but superior for tolerability when compared with a standard treatment; tolerability is examined in secondary outcomes, including time to treatment failure for adverse effects. Powering the study for non-inferiority would also provide sufficient power to detect important differences between treatment policies.

TABLE 1 Method of categorising whether or not treatment failure is an event

Reason for withdrawal from randomised drug/addition of a new anti-seizure medication	Categorised as event or censored in 'time to treatment failure'	ISC/UAR
Inadequate seizure control	Event	ISC
UAR	Event	UAR
Remission of epilepsy categorised by clinician (regardless of length in remission)	Censored	–
Remission of epilepsy categorised by patient (> 12 months' remission from seizures)	Censored	–
Remission of epilepsy categorised by patient[a] (< 12 months' remission from seizures)	Event	UAR
Diagnosis no longer epilepsy	Censored	–
Study withdrawal – consent withdrawn[b]	Censored	–
Death (unrelated to epilepsy/anti-seizure medication)[c]	Censored	–
Death (related to epilepsy/anti-seizure medication)[c]	Event	Could be ISC, UAR or neither
Moved from area	Censored	–
Patient non-compliant/did not wish to continue[d]	Event	Could be ISC, UAR or neither
Perceived adverse effect (e.g. pregnant or planning pregnancy)	Event	UAR

a Patients' decision to withdraw before 12 months' freedom from seizures is likely to be highly influenced by side effects of the drug or the 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 Relatedness recorded in death CRF.
d Further information was sought if a patient withdrew because of 'non-compliance', as the underlying reason could be UAR, ISC or remission of epilepsy.

The International League Against Epilepsy (ILAE) Commission on Antiepileptic Drugs defined limits of equivalence of ± 10% for the primary outcome in anti-seizure medication monotherapy studies.[41] However, the Commission was not explicit as to whether this should be on the hazard ratio (HR) or absolute scale. No empirical work had been undertaken to underpin the choice of equivalence or non-inferiority margins in epilepsy trials. The chief investigator had given numerous seminars and lectures in the UK and elsewhere about epilepsy trial methodology, and the audience had typically voted for a margin of 10% around absolute differences between anti-seizure medications for monotherapy studies when given examples of margins ranging from 20% to 5%. Communicating treatment differences to patients on a HR scale is also difficult compared with a discussion of absolute differences at specific time points. Given that the ultimate purpose of the SANAD II trial is to provide information that patients and clinicians can use to help them to make treatment decisions, the non-inferiority margin for the SANAD II trial was been chosen according to absolute differences.

Calculations were informed by the SANAD I study, which estimated the 12-month remission-free probability (at 24 months) as 0.43 (exponential hazard rate of 0.0352) for lamotrigine (focal standard), and 0.31 (exponential hazard rate of 0.0488) for valproate (generalised and unclassified epilepsy standard). The calculations assumed a HR of 1.0, 80% power, and allowance for approximately 5% losses to follow-up throughout, as observed in the SANAD I trial. For the focal epilepsy trial, two primary comparisons were of interest (i.e. levetiracetam vs. lamotrigine, and zonisamide vs. lamotrigine); therefore, the one-sided

significance level was divided by 2 (one-sided alpha 0.0125). Assuming a 10% absolute difference in survival probability, the non-inferiority margin on the HR scale was:

$$\ln(0.43)/\ln(0.53) = 1.329. \quad (1)$$

After adjusting for 5% losses to follow-up, 330 patients were required in each of the three treatment groups (i.e. a total of 990 patients). For the generalised or unclassified epilepsy trial, there was only one comparison of interest (levetiracetam vs. valproate). Assuming a 10% absolute difference in survival probability, the non-inferiority margin on the HR scale was as follows for the trial in generalised or unclassified epilepsy:

$$\ln(0.31)/\ln(0.41) = 1.314. \quad (2)$$

Therefore, with a one-sided alpha of 0.025, 260 patients were required in each of the two treatment groups, allowing for 5% losses to follow-up (i.e. a total of 520 patients). The total number of patients required for both trials was 1510. The sample size was calculated using nQuery software (Statistical Solutions Ltd, Cork, Ireland).

Statistical analysis

The statistical analysis and reporting of the SANAD II trial were undertaken in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines[42] and the International Conference on Harmonisation E9 guidelines.[43] Primary analyses were undertaken on an intention-to-treat (ITT) basis, including all randomised patients retained in their randomised treatment groups. The statistical and health economic analysis plans were developed before conducting final analyses. Analyses were conducted using SAS® software (version 9.4; SAS Institute, Cary, NC, USA).

All analyses were conducted separately for the trial in focal epilepsy and the trial in generalised and unclassified epilepsy. A 97.5% two-sided confidence interval (CI) was used for the primary outcome analysis for the focal epilepsy trial (see *Sample size* for justification). All other CIs (focal epilepsy trial and generalised or unclassified epilepsy trial) were calculated at the 95% level (two-sided), with a two-sided p-value of ≤ 0.05 used to declare statistical significance for all analyses. No formal adjustment was made for multiple testing of secondary outcomes, but conclusions drawn from the analysis of all secondary outcomes would be cautionary unless the p-value was < 0.001.

The time-to-event outcomes were summarised using Kaplan–Meier curves for each treatment group and explored using two different Cox proportional hazards regression models: (1) including the treatment effect only using an indicator variable and (2) including the treatment effect together with minimisation factors included as indicator variables for gender (male or female), number of seizures prior to randomisation (two, three to five, or six or more) and random effects for centre. The assumption of proportional hazards was investigated by examining Schoenfeld residual plots, and incorporating time-dependent covariates in all models. If the residuals were not time dependent and the parameter estimate for the time-dependent covariate was not significant at the 5% level, then the assumption of proportional hazards was assumed to hold; otherwise, an additional extended Cox model with the addition of time-dependent covariates was used. The HR and relevant CI (95% CI unless indicated otherwise) are presented for the comparison of lamotrigine with levetiracetam (focal epilepsy trial), lamotrigine with zonisamide (focal epilepsy trial) and valproate with levetiracetam (generalised or unclassified epilepsy trial). For the primary outcome (12-month remission) non-inferiority hypothesis, the upper limit of the 97.5% CI should be < 1.329 to conclude non-inferiority for the focal epilepsy trial, whereas the upper limit of the 95% CI should be < 1.314 to conclude non-inferiority for the generalised and unclassified epilepsy trial.

A per-protocol (PP) analysis of the primary outcome of time to 12-month remission was also undertaken using a Fine and Gray model,[44] with treatment failure included as a competing risk, and censoring participants with drug failure (withdrawn from study or drug or other anti-seizure medication added) before achieving a period of remission. This analysis excluded participants with major protocol deviations, those subsequently given an alternative diagnosis to epilepsy and those who did not receive the drug at all.

For time to treatment failure, a competing risks analysis, using the Fine and Gray model,[44] was undertaken to assess the two main reasons for treatment failure (i.e. ISC and UAR).[45] Cumulative incidence curves are presented for each treatment group.

The difference in QoL measures between treatment groups was estimated for each population (child/adult/parent–carer), and for each outcome applicable within that population. This was carried out by fitting a repeated measures random-effects model, with baseline QoL variable as a covariate, along with treatment group and time in days, using spatial power covariance structure for repeated measures (appropriate for repeated measures that can be unevenly spaced), and unstructured covariance for the random effect.[46]

Analysis sets for the summary of ARs include all patients who received any dose of a study drug. All ARs and serious adverse reactions (SARs) were coded using the MedDRA dictionary to the most appropriate lower-level term, preferred term and higher-level System Organ Classification. The number (and percentage) of patients experiencing each reaction, and the number (and percentage) of occurrences of each reaction are presented with no formal statistical testing undertaken.

Interim monitoring was carried out by an Independent Data and Safety Monitoring Committee (IDSMC), meeting approximately annually. This included analyses of the primary outcome and five of the secondary outcomes (all using the Haybittle–Peto approach).[47]

Health economics

The economic analysis was conducted from the perspective of the NHS and Personal Social Services in the UK. The primary economic analysis compared the costs and consequences of each anti-seizure medication over the first 24 months post randomisation. An analysis at an extended 48-month time horizon was planned for those participants followed up for ≥ 4 years.

The within-trial economic analysis was performed using individual, patient-level data from the SANAD II trial. Cost-utility analyses were conducted to estimate incremental cost-effectiveness ratios, expressed as costs per quality-adjusted life-years (QALYs) gained.

The health economic analysis was carried out in Stata® IC version 13 (StataCorp LP, College Station, TX, USA), and reported according to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement.[48]

Data sources

Resource use

Participants' use of resources was considered in four broad categories: (1) resource use associated with secondary care [inpatient, outpatient, accident and emergency (A&E)], (2) other health-care and social services resource use (primary care, community services), (3) consumption of anti-seizure medication and (4) use of other medications.

The measurement of resource use was based on complementary approaches, using data collected as part of the trial and as part of routine care. Resource use postal questionnaires, completed by the parent or carer for participants aged < 16 years, included a modified CSRI based on that from the SANAD I trial.[37,49,50] This CSRI was used to collect information on participants' use of health service resources, personal social services and medicines. The questions pertained to contacts with health professionals at the GP surgery, in the hospital and in the community; the use of emergency services; and any tests or investigations that the patients may have had. The questionnaires were initially administered at 3, 6 and 12 months and annually thereafter (up to 60 months); however, from version 7 of the protocol onwards, this questionnaire was also provided during outpatient visits to aid completeness. The questionnaires completed following visits were matched to respective time points for analysis.

In all cases, participants were asked to report their primary and secondary care and social services resource use for the 3-month period prior to completing the questionnaire, and to report their medicines use over a 4-week period prior to completing the questionnaire because of the additional complexity in the recall. The self-report questionnaires contained free-text sections that allowed participants to record any resource use that would not otherwise be captured by the questionnaire. During analysis, these records of resource use were assessed for duplication against the resources captured by the questionnaire, and any relevant, non-duplicated resources were extracted.

Self-report data were therefore available for months 0–3, 3–6, 9–12 and 21–24. Self-reported resource use for year 1 was estimated by multiplying the resource use from months 9–12 by two, and adding the resource use reported for months 0–3 and 3–6. Self-reported resource use for year 2 was estimated by multiplying resource use for months 21–24 by four, and similarly for years 3, 4 and 5. Participants' use of concomitant medicines was multiplied by three (owing to the shorter, 4-week recall period), before estimation following the same method.

With respect to the consumption of anti-seizure medications, the type of drug and the doses taken were recorded directly within CRFs.

Routine HES data were the primary source of participants' use of secondary care resources over the trial period. HES data were requested from NHS Digital (for patients in England)[51] and from the Secure Anonymised Information Linkage databank (for patients in Wales),[52] but were not obtained for patients in Scotland or Northern Ireland. HES provided Health Resource Group (HRG) data on the type of care that patients receive at a ward level, outpatient visits and A&E admissions. HES data were used as the source for baseline resource use and costs, based on the 6 months prior to randomisation. Adjustments were made when hospital episodes overlapped with randomisation dates to apportion the resource use to the periods prior, and subsequent to randomisation.

All resource use was measured, irrespective of whether or not it was epilepsy related.[53]

Unit costs

Resource use was valued in monetary terms (Great British pounds) using sources of national unit costs.[24,54–56]

Health Resource Groups were used as the main currency for inpatient stays, outpatient visits and A&E attendance. For data pertaining to participants from Wales, an initial mapping step was performed using the Welsh NHS Data dictionary.[57] Subsequently, HRG codes were obtained from the HES data using the NHS Digital costing grouper.[58] Unit costs were allocated based on the latest available national schedule.[54]

Unit costs for primary care and community care were taken from the compendium of *Unit Costs of Health and Social Care 2019*.[55] Unit costs and their sources relating to items within the self-report

questionnaire are presented in *Appendix 4*, *Table 45*. Unit costs relating to the most commonly reported HRGs are presented in *Appendix 4*, *Table 46*.

Total costs for resource use were calculated by multiplying the unit cost per item by the recorded number of times that each resource was used.

Medication costs were taken from the *British National Formulary* using drug tariff prices, when available,[24] or the NHS indicative price, and the Prescription Costs Analysis for England.[56] Unit costs for trial anti-seizure medications are presented in *Appendix 4*, *Table 47*. Unless otherwise specified in the data, children aged ≥ 9 years were assumed to be prescribed tablets or capsules, whereas children aged ≤ 8 years were assumed to be prescribed an alternative form (e.g. solution, dispersible), when available.

The cost of each medicine was calculated by assessing the price per dose and multiplying this by the quantity prescribed (e.g. number of tablets, capsules, inhalers or prefilled syringes) and the number of days of treatment.

All costs are at 2019/20 prices and were discounted in the base-case analysis at the NICE-recommended rate of 3.5% per annum.[59]

Health utilities

The primary health outcome measure for the economic analysis was the QALY, generated from utility data measured using the EQ-5D-3L questionnaire.[60] The secondary economic outcome measures were the EQ-VAS and an epilepsy-specific utility measure: the NEWQOL-6D.[61]

The EuroQol-5 Dimensions (EQ-5D) descriptive system includes five dimensions, relating to mobility, self-care, usual activities, pain and discomfort, and anxiety. For the EQ-5D-3L and EQ-5D-3L-Y, each dimension is measured against three statements (i.e. no problems, some problems or extreme problems), scored 1, 2 and 3, respectively. The NEWQOL-6D is an epilepsy-specific measure that includes domains of worry, depression, memory, concentration, control and stigma. Responses are measured according to four categories. Utility scores are obtained from the EQ-5D-3L-Y, EQ-5D-3L, EQ-5D-3L proxy and NEWQOL-6D using UK tariff values.[61,62]

For participants aged 8–15 years, self-reported responses to the EQ-5D-3L-Y or, if not available, proxy questionnaire responses (EQ-5D-3L and NEWQOL-6D) completed by a parent or carer were used. For participants aged 5–7 years, only proxy questionnaires were administered. All participants aged ≥ 8 years were administered the EQ-VAS.

All economic outcome measures were completed during the baseline visit and annually thereafter (up to 60 months), and, from version 7 of the protocol onwards, were also provided during outpatient visits to aid completeness. Utility scores at 365 days (12 months) and at 730 days (24 months) were interpolated, based on recorded utility scores and actual dates of questionnaire completion. QALY profiles were derived from these utilities, estimated based on the area under the curve (AUC), assuming the trapezoidal rule, using all available data. The QALYs derived from the secondary health economic outcomes (EQ-VAS and NEWQOL-6D) were estimated in the same way, based on AUC.

All QALYs were discounted at the NICE-recommended rate of 3.5% per annum.[59]

Data analysis

Analysis consisted of all randomised participants, which is consistent with the ITT approach. All statistical tests were two-sided, with CIs and central ranges (CRs) reported at 97.5% for the trial in focal epilepsy and 95% for the trial in generalised or unclassified epilepsy.

The costs relating to secondary care were primarily sourced from HES data, but where these data were not available costs were supplemented with resource use recorded in the self-report questionnaires. Primary and community care costs and concomitant medication costs were also taken from the resource use questionnaires. If resource use questionnaires were returned but no response was provided for a given resource, then use of that resource was assumed to be zero. If participants indicated that they had used a resource but had not given a number for how many times the resource was used, then the number was assumed to be 1. The data relating to anti-seizure medications were taken from the baseline and follow-up CRFs. Missing dose data were assigned according to previous or subsequent prescriptions, based on questions relating to dose changes, or, if these were unavailable, from the *British National Formulary* recommended doses.

Data were examined for missingness and appropriate methods were applied depending on the level of missingness and likely mechanism of missingness.[63] Missing cost and QALY data were imputed using multiple imputation with chained equations.[63] To maximise data use, data were imputed at the level of utility scores (EQ-5D, EQ-VAS) at baseline and at 12 and 24 months; primary care, community care and concomitant medications costs at 3, 6, 12 and 24 months; and admitted patient care, outpatients, A&E and anti-seizure medication costs at 12 and 24 months. Owing to the return dates of questionnaires not coinciding exactly with 365 and 730 days, utility values for 365 and 730 days were interpolated (using linear interpolation). Baseline costs (relating to admitted patient care, outpatients, accident and emergency) were also imputed for those participants for whom HES data were not available. Imputation models were generated using predictive mean matching, and data were imputed by randomised treatment group. Variables pertaining to epilepsy classification, seizure type, age, gender, primary outcome and treatment failure were included within the imputation models. Imputation models for baseline measures omitted post-baseline outcomes to preserve randomisation. The number of imputations required was based on the level of missingness, according to the fraction of missing information.[64]

Based on the imputed data, total costs and QALYs during the course of the trial were calculated, with summary statistics generated by randomised treatment group. The differences between treatment groups were compared with reference to bootstrapped CRs, based on 10,000 replications.

Total costs and QALYs (at 24 months) were adjusted for any imbalances in baseline costs and utilities respectively, and clinical or demographic variables (age, sex, epilepsy classification, with centre as random effects), using ordinary least squares regressions.[64,65] Ordinary least squares was considered to be appropriate given the large sample size.[66]

Incremental analysis

Differences in estimated mean QALYs and costs by treatment group were combined to calculate incremental cost-effectiveness ratios (ICERs). Interventions were ranked according to their effectiveness (from highest to lowest QALYs), and dominance and extended dominance were determined. The ICER was calculated for non-dominated interventions as:

$$\text{ICER} = (\text{difference in costs})/(\text{difference in QALYs}). \quad (3)$$

Net health benefits (NHB) and incremental net health benefits (INHB) were also calculated at the £20,000 per QALY and £30,000 per QALY thresholds, according to the following formulae:

$$\text{NHB} = (\text{QALYs}) - (\text{costs})/\lambda, \quad (4)$$

$$\text{INHB} = (\text{difference in QALYs}) - (\text{difference in costs})/\lambda, \quad (5)$$

where λ is the cost-effectiveness threshold.[67]

The base-case was defined as being from the perspective of the NHS and Personal Social Services, adopting a 2-year time horizon, and based on the imputed data set of the ITT population, with adjusted costs and QALYs.

The protocol-specified cost-effectiveness analyses, based on the incremental cost per seizure avoided and per 12-month remission, were not conducted because there were insufficient data on likely acceptable thresholds of cost-effectiveness from other economic assessments of anti-seizure medicines.

Sensitivity analysis

Several sensitivity analyses were conducted to assess the robustness of the base-case results to key assumptions. These:

- used discount rates of 0% and 6% per annum for costs and QALYs
- were an unadjusted analysis (i.e. based on mean costs and QALYs, with no regression)
- used results for complete-case cost and QALY data (i.e. those without missing data) to identify the impact of missing data and imputation
- were based on the population as the PP cohort
- used QALYs derived from the NEWQOL-6D and EQ-VAS
- treated blank values in resource use questionnaires as missing, rather than zero.

A bootstrap analysis was conducted to consider the joint uncertainty in incremental costs and QALYs. This was represented as a cost-effectiveness plane and as a cost-effectiveness acceptability curve, illustrating the probability of each treatment being cost-effective for a given cost-effectiveness threshold.[68]

Subgroup analysis

Subgroup analyses were conducted to investigate how cost-effectiveness varied by age, according to whether participants were adults (i.e. aged $\geq$ 16 years) or children (aged $<$ 16 years).

Patient and public involvement

The SANAD II trial was designed in collaboration with Epilepsy Action (Leeds, UK), which consulted its members. A patient and public involvement representative sat on the Trial Steering Committee (TSC) and attended regular meetings during the trial. The trial team will collaborate with Epilepsy Action on dissemination of results to the public.

Protocol amendments

During the course of the SANAD II trial, a number of amendments were made to the trial protocol. These are further detailed in *Appendix 2*. Each amendment was assessed by the Trial Management Group (TMG), TSC, co-sponsors and funder prior to being submitted for approval. Approval for amendments was sought from the Research Ethics Committee, MHRA (if appropriate) and (post 2015) from the Health Research Authority.

Trial funder

The SANAD II trial was funded by the NIHR Health Technology Assessment programme (09/144/09).

Trial co-sponsors

The SANAD II trial was co-sponsored by the University of Liverpool and the Walton Centre NHS Foundation Trust.

Trial management and quality assurance

The SANAD II trial was managed by the LCTC. A risk assessment was performed by the LCTC in conjunction with co-sponsors and the chief investigator. The risk assessment indicated that the SANAD II trial was low risk. As such, monitoring/quality assurance was carried out centrally. This included confirming informed consent; the MACRO database containing predefined ranges that flagged data queries; and the trial statistician producing 6-monthly reports to look for errors, inconsistencies in data, assess safety and to highlight any protocol deviations.

Trial oversight

The SANAD II trial was overseen by the TMG, TSC and IDSMC.

Ethics considerations, regulatory requirements and research governance framework

The SANAD II trial was conducted in accordance with the European Clinical Trials Directive,[69] ICH GCP Guidelines,[70] the Declaration of Helsinki,[71] UK Policy Framework for Health and Social Care Research,[72] and the Medicines for Human Use (clinical trials) regulations (2004).[73] The SANAD II trial was issued a EudraCT number (2012-001884-64) and approved by the MHRA on 22 May 2012 ('effective date'). We also sought and received approval from the North West – Liverpool East Research Ethics Committee for the SANAD II trial to proceed. This was granted on 7 June 2012.

Research Ethics Committee approval was sought for all amendments made to the protocol. MHRA approval was sought for all amendments that related to the trial investigational medicinal products. The SANAD II trial was brought under the HRA umbrella in 2016.

Chapter 3 Focal epilepsy: clinical results

Recruitment and baseline characteristics

The first participant was randomised on 2 May 2013 and the last participant on 20 June 2017 (see *Appendix 3*, *Figure 23*), after which every effort was made to follow the trial cohort for a further 2 years; the last participant follow-up visit was on 17 October 2019. Sixty-five UK centres recruited between 1 and 130 patients each, and randomised a total of 990 participants: 330 to start treatment with lamotrigine, 332 to start treatment with levetiracetam and 328 to start treatment with zonisamide (*Figure 2*). Baseline characteristics were well balanced across treatment groups (*Table 2* and see *Appendix 3*, *Table 31*). The mean age of participants was 39.3 years [standard deviation (SD) 21.2 years] and

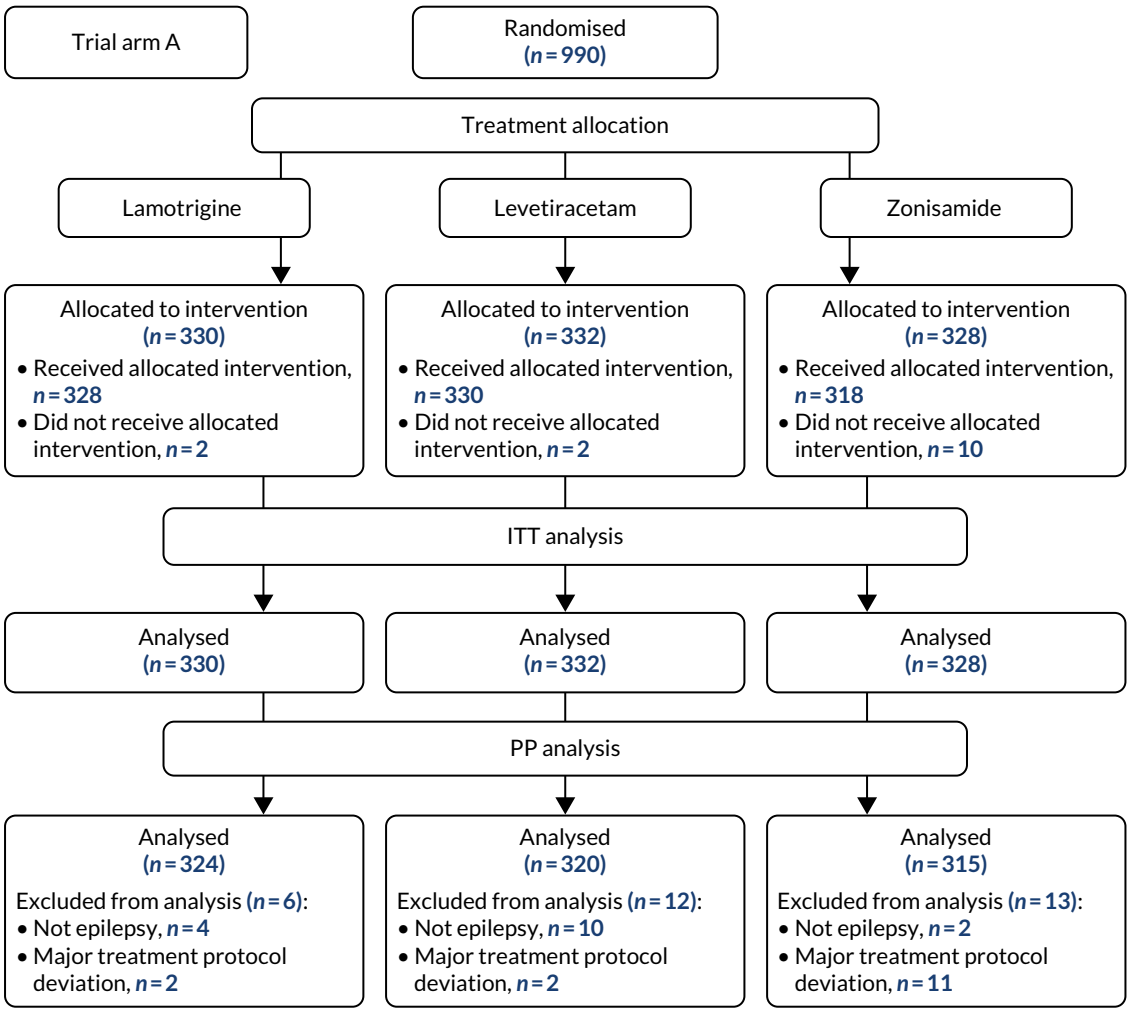

FIGURE 2 The CONSORT participant flow diagram: focal epilepsy trial.

TABLE 2 Baseline characteristics

Characteristic	Lamotrigine group (*N* = 330)	Levetiracetam group (*N* = 332)	Zonisamide group (*N* = 328)	Total (*N* = 990)
Age (years)				
Mean (SD)	40.1 (21.7)	37.8 (20.1)	39.9 (21.6)	39.3 (21.2)
Range	5.1–91.9	5.0–87.6	5.0–89.1	5.0–91.9
Gender, *n* (%)				
Male	186 (56.4)	190 (57.2)	185 (56.4)	561 (56.7)
History, *n* (%)				
Learning disability	15 (4.5)	16 (4.8)	14 (4.3)	45 (4.5)
Febrile convulsions	10 (3.0)	19 (5.7)	15 (4.6)	44 (4.4)
Acute symptomatic seizures	6 (1.8)	9 (2.7)	4 (1.2)	19 (1.9)
History of epilepsy in primary relatives	32 (9.7)	35 (10.5)	40 (12.2)	107 (10.8)
Neurological deficit	12 (3.6)	20 (6.0)	12 (3.7)	44 (4.4)
Previous or current neurological disorder, *n* (%)				
Stroke/cerebrovascular	17 (5.2)	16 (4.8)	14 (4.3)	47 (4.7)
Cerebral haemorrhage	2 (0.6)	5 (1.5)	7 (2.1)	14 (1.4)
Intracranial surgery	4 (1.2)	6 (1.8)	10 (3.0)	20 (2.0)
Head injury	4 (1.2)	7 (2.1)	7 (2.1)	18 (1.8)
Meningitis/encephalitis	6 (1.8)	5 (1.5)	6 (1.8)	17 (1.7)
Cortical dysplasia/developmental anomaly	1 (0.3)	3 (0.9)	(0.0)	4 (0.4)
Other	27 (8.2)	24 (7.2)	18 (5.5)	69 (7.0)
Epilepsy syndrome, *n* (%)				
Benign childhood epilepsy with centrotemporal spikes	9 (2.7)	15 (4.5)	10 (3.0)	34 (3.4)
Childhood epilepsy with occipital paroxysms	(0.0)	1 (0.3)	(0.0)	1 (0.1)
Temporal lobe	134 (40.6)	110 (33.1)	111 (33.8)	355 (35.9)
Frontal lobe	21 (6.4)	21 (6.3)	20 (6.1)	62 (6.3)
Parietal lobe	7 (2.1)	8 (2.4)	5 (1.5)	20 (2.0)
Occipital lobe	7 (2.1)	12 (3.6)	2 (0.6)	21 (2.1)
Focal epilepsy localisation not specified	152 (46.1)	165 (49.7)	182 (55.5)	499 (50.4)
Other epilepsy syndrome	3 (0.9)	1 (0.3)	1 (0.3)	5 (0.5)
Seizure history, median (IQR)				
Total number of seizures reported	6 (3–29)	6 (3–22)	6 (3–23)	6 (3–24)
Days since first seizure	333 (110–1090)	318 (119–985)	328 (120–1097)	327 (114–1035)
Days since most recent seizure	13 (3–41)	13 (3–35)	11 (3–34)	13 (3–36)

IQR, interquartile range.

177 (17.9%) participants were aged < 18 years. There was a predominance of males (56.7%), 4.5% of participants had a learning disability, 16.5% had a previous or current neurological disorder, 10.8% a first-degree relative with epilepsy and 4.4% had a history of febrile convulsions. A total of 35.9% of participants were classified with temporal lobe epilepsy, 6.3% with frontal lobe epilepsy, 2.1% with occipital lobe epilepsy, 2.0% with parietal lobe epilepsy and 50.4% with focal epilepsy where localisation was not specified. The median number of seizures before randomisation was 6 [interquartile range (IQR) 3–24] and participants were randomised a median of 13 days (IQR 3–36 days) after their most recent seizure.

The median number of days of follow-up was 462.5 (IQR 365–777 days) in the lamotrigine group, 449.5 (IQR 365–824) days in the levetiracetam group and 447 (IQR 365–730) days in the zonisamide group, with completeness of follow-up statistics for the primary outcome of 77.2% in the lamotrigine group, 78.3% in the levetiracetam group and 75.6% in the zonisamide group (see *Appendix 3*, *Table 30* and *Figure 24*).

Time to 12-month remission

Estimates from the primary and secondary analyses are provided in *Table 3*. For the ITT analysis of time to 12-month remission, there is insufficient evidence to conclude non-inferiority of levetiracetam compared with lamotrigine, as the 97.5% confidence interval for the HR (1.18, 97.5% CI 0.95 to 1.47, unadjusted; 1.13, 97.5% CI 0.91 to 1.41, adjusted) includes the predefined non-inferiority margin of 1.329, but there was sufficient evidence to conclude non-inferiority of zonisamide compared with lamotrigine (HR 1.03, 97.5% 0.83 to 1.28, unadjusted; 1.01, 97.5% CI 0.81 to 1.25, adjusted). There was no evidence of violation of the assumption of proportional hazards ($p = 0.90$). We also present the annual 12-month remission probabilities (*Table 4*); for example, we estimate that, at 2 years' follow-up, compared with the lamotrigine group, the proportion of participants who had achieved remission was 5% lower (97.5% CI −13% to 3%) in the levetiracetam group and 1% lower (97.5% CI −9% to 7%) in the zonisamide group. The Kaplan–Meier estimates of the median number of days to achieve 12-month remission were 516 (97.5% CI 457 to 577) days in the lamotrigine group, 588 (97.5% CI 472 to 706) days in the levetiracetam group and 530 (97.5% CI 453 to 601) days in the zonisamide group (*Figure 3*).

The PP analyses for time to 12-month remission excluded patients with major protocol deviations (1.5%) and patients who were later diagnosed as 'not epilepsy' (1.6%) and accounted for treatment failures prior to achieving 12-month remission (lamotrigine group, 24%; levetiracetam group, 35%; zonisamide group, 39%) in a competing risks analysis (*Figure 4*). The results indicate that lamotrigine is superior to both levetiracetam (HR 1.32, 97.5% CI 1.05 to 1.66) and zonisamide (HR 1.37, 97.5% CI 1.08 to 1.73).

TABLE 3 Hazard ratio estimates for time to 12-month remission: lamotrigine vs. levetiracetam vs. zonisamide for focal epilepsy

Model and analysis set	Lamotrigine vs. levetiracetam HR (97.5% CI)	Lamotrigine vs. zonisamide HR (97.5% CI)
Primary analysis: Cox model with treatment (ITT)	1.189 (0.96 to 1.47)	1.03 (0.83 to 1.28)
Cox model with treatment (ITT), gender, number of seizures and centre as random effects	1.13 (0.91 to 1.41)	1.01 (0.81 to 1.25)
Fine and Gray model[44] with treatment (PP)	1.32[a] (1.05 to 1.66)	1.37[a] (1.08 to 1.73)

a Ratio of rate of occurrence of 12-month remission in patients who are currently event free or who have previously failed randomised treatment.

Note
HR > 1 indicates benefit to lamotrigine.

TABLE 4 Annual 12-month remission probability estimates from Kaplan–Meier analysis: lamotrigine vs. levetiracetam vs. zonisamide for focal epilepsy

Probability estimate	Events/total	Year 1	Year 2	Year 3	Year 4	Year 5
Number at risk						
Lamotrigine	222/330	291	92	34	12	2
Levetiracetam	204/332	293	107	57	22	5
Zonisamide	209/328	284	92	29	10	2
Percentage of 12-month remission (95% CI)						
Lamotrigine		34 (29 to 39)	63 (58 to 69)	79 (74 to 84)	82 (77 to 88)	86 (80 to 92)
Levetiracetam		37 (32 to 43)	59 (53 to 64)	70 (64 to 76)	77 (71 to 82)	79 (73 to 85)
Zonisamide		35 (29 to 40)	63 (57 to 68)	78 (72 to 84)	84 (78 to 90)	91 (83 to 100)
Difference in percentage of 12-month remission compared with lamotrigine (95% CI)						
Levetiracetam		3 (−5 to 11)	−5 (−13 to 3)	−9 (−17 to −2)	−6 (−14 to 2)	−7 (−16 to 1)
Zonisamide		1 (−7 to 9)	−1 (−9 to 7)	−1 (−9 to 7)	2 (−6 to 10)	5 (−5 to 16)

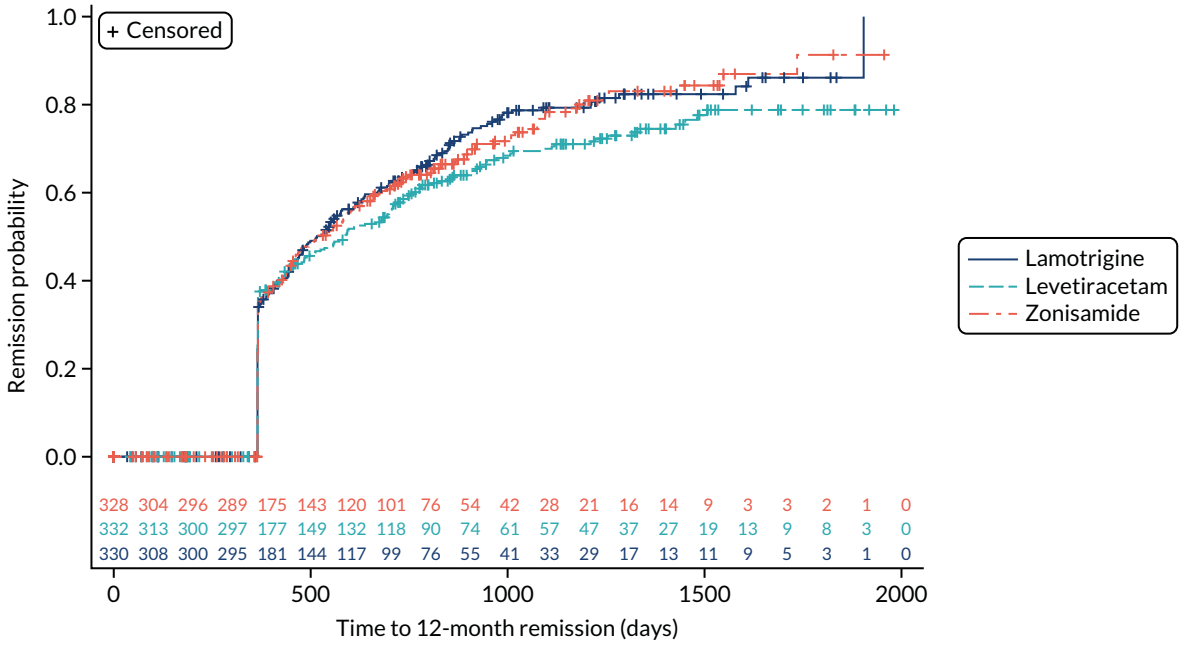

FIGURE 3 Kaplan–Meier plot of time to 12-month remission: lamotrigine vs. levetiracetam vs. zonisamide for focal epilepsy.

Additional prespecified sensitivity analyses, the results of which are shown in *Appendix 3*, *Table 32*, did not change the conclusions of the primary analyses.

Time to 24-month remission

The ITT analysis of time to 24-month remission (*Figure 5*) indicates no significant difference between initiating treatment with lamotrigine or levetiracetam (HR 1.04, 95% CI 0.81 to 1.33) or between initiating treatment with lamotrigine of zonisamide (HR 0.96, 95% CI 0.75 to 1.23).

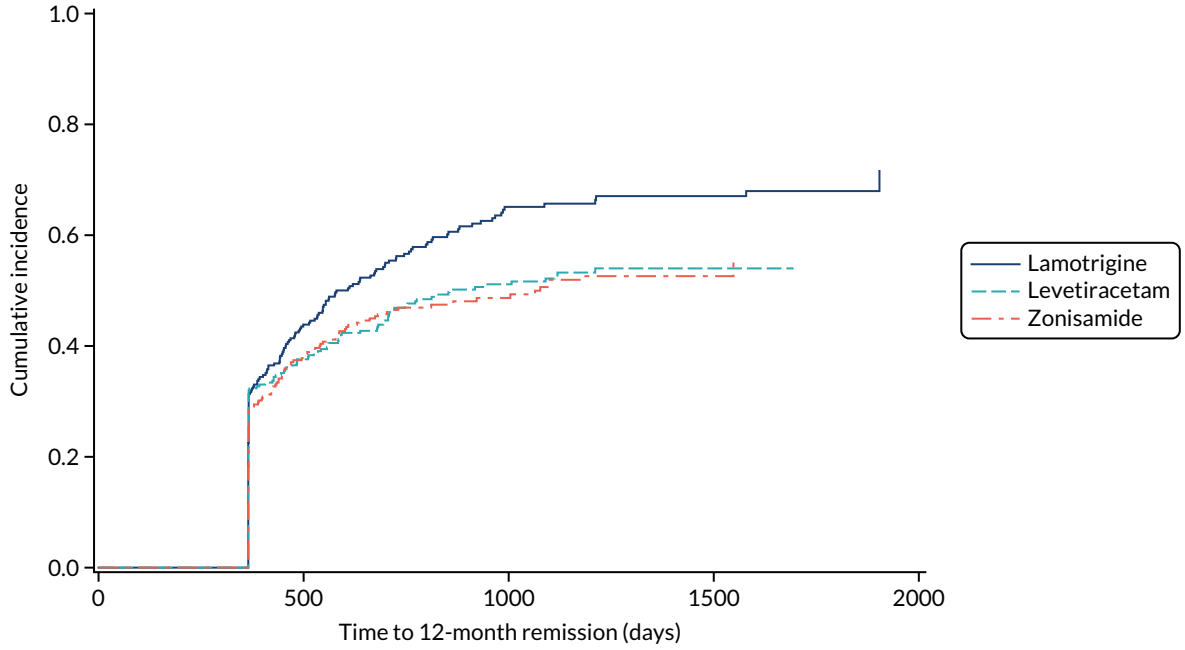

FIGURE 4 Cumulative incidence of time to 12-month remission, PP competing risks analysis: lamotrigine vs. levetiracetam vs. zonisamide for focal epilepsy.

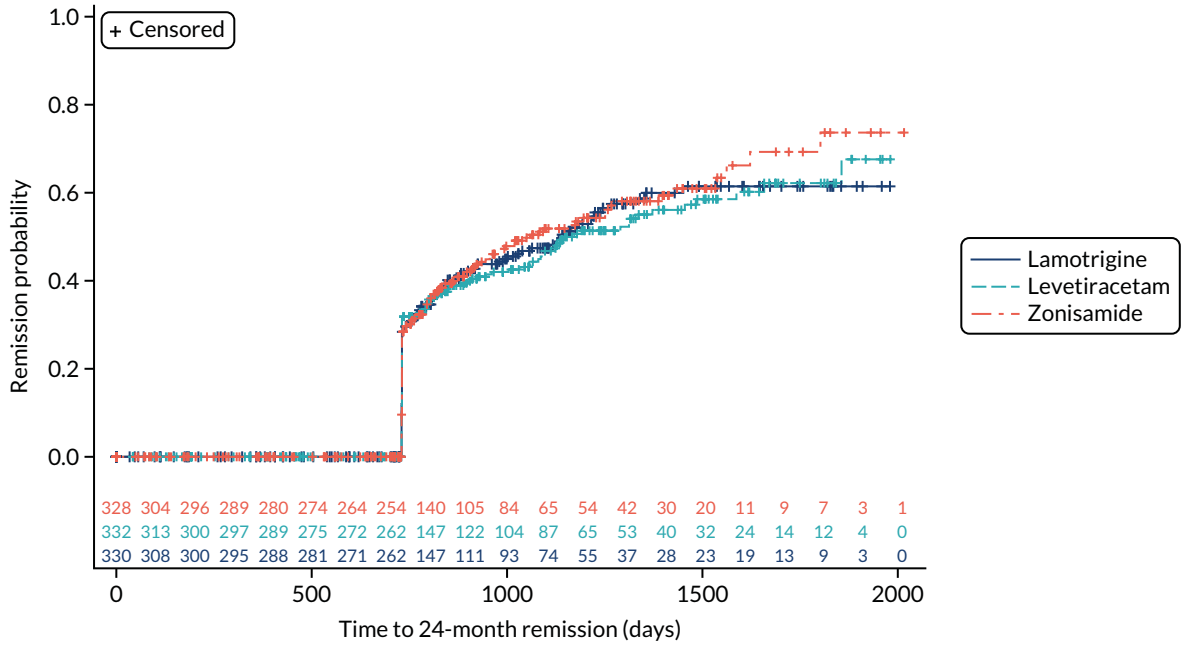

FIGURE 5 Kaplan–Meier plot of time to 24 month remission: lamotrigine vs. levetiracetam vs. zonisamide for focal epilepsy.

Time to first seizure

The ITT analysis of time to first seizure (*Figure 6*) indicates no significant difference between initiating treatment with lamotrigine or levetiracetam (HR 1.07, 95% CI 0.89 to 1.29) or between initiating treatment with lamotrigine of zonisamide (HR 1.04, 95% CI 0.86 to 1.25).

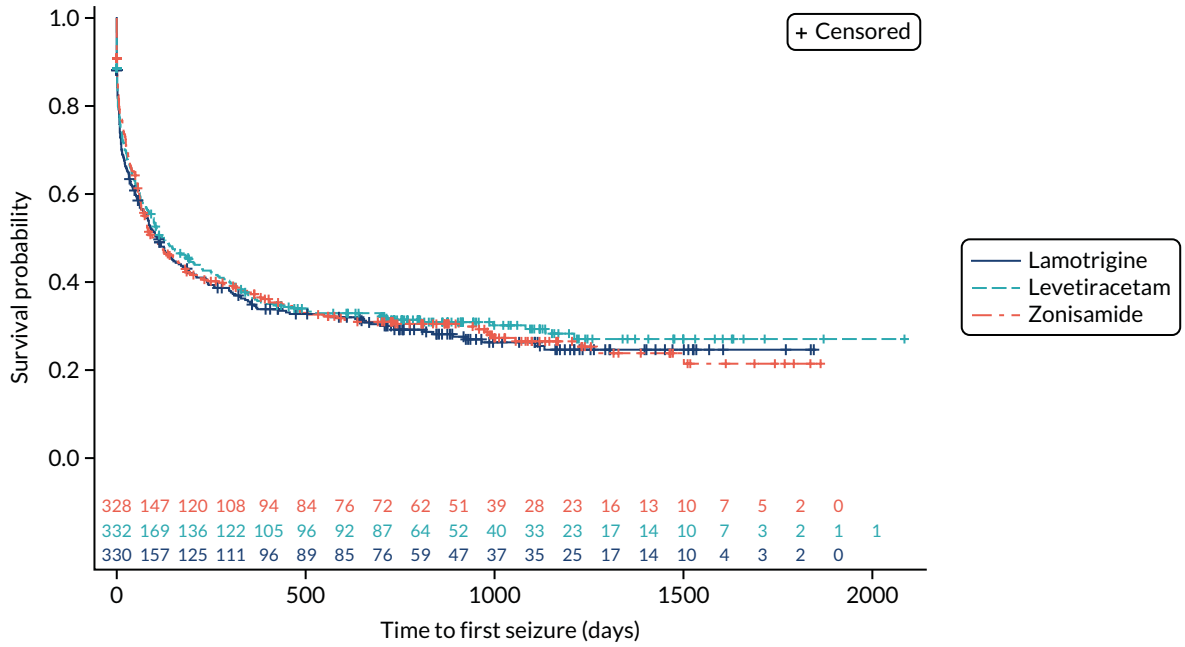

FIGURE 6 Kaplan–Meier plot of time to first seizure: lamotrigine vs. levetiracetam vs. zonisamide for focal epilepsy.

Time to treatment failure

The analysis of overall time to treatment failure for any reason (*Figure 7*) indicates a significant advantage of lamotrigine when compared with both levetiracetam (HR 0.60, 95% CI 0.46 to 0.77) and zonisamide (HR 0.46, 95% CI 0.36 to 0.60), with no evidence to suggest violation of the assumption of proportional hazards ($p = 0.77$). *Table 5* provides annual treatment failure rates and differences in failure rates between lamotrigine and both levetiracetam and zonisamide. At 2 years, there was a 16% (95% CI 8% to 23%) difference in the treatment failure rate on levetiracetam and lamotrigine and a 23% (95% CI 15% to 30%) difference between zonisamide and lamotrigine.

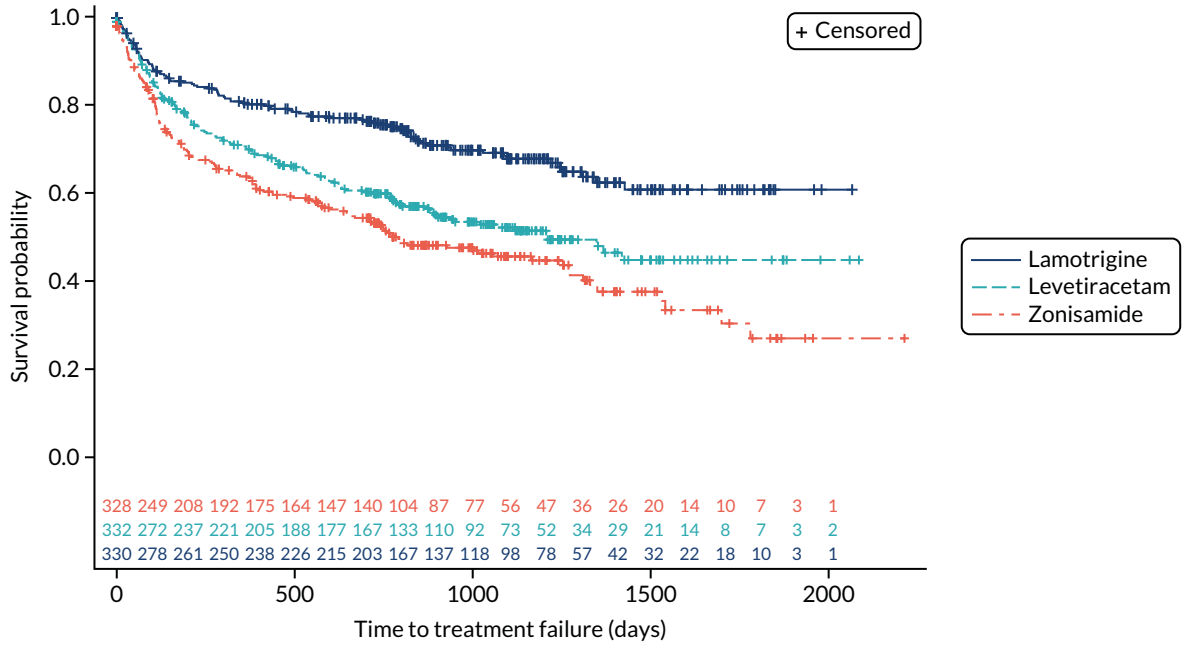

FIGURE 7 Kaplan–Meier plot of time to treatment failure: lamotrigine vs. levetiracetam vs. zonisamide for focal epilepsy.

TABLE 5 Annual survival probability estimates from Kaplan–Meier analysis of treatment failure: lamotrigine vs. levetiracetam vs. zonisamide for focal epilepsy

Probability estimate	Events/total	Year 1	Year 2	Year 3	Year 4	Year 5
Number at risk						
Lamotrigine	97/330	241	192	101	36	8
Levetiracetam	146/332	212	157	74	25	7
Zonisamide	167/328	185	128	59	23	7
Percentage without failure (95% CI)						
Lamotrigine		80 (75 to 84)	76 (71 to 80)	68 (62 to 73)	61 (53 to 68)	61 (53 to 68)
Levetiracetam		70 (65 to 75)	60 (54 to 65)	52 (46 to 58)	45 (37 to 52)	45 (37 to 52)
Zonisamide		64 (58 to 69)	53 (47 to 59)	45 (39 to 52)	37 (30 to 45)	27 (16 to 37)
Difference in percentage with failure compared with lamotrigine (95% CI)						
Levetiracetam		10 (3 to 17)	16 (8 to 23)	16 (7 to 24)	16 (5 to 27)	16 (5 to 27)
Zonisamide		16 (9 to 23)	23 (15 to 30)	22 (14 to 30)	23 (13 to 34)	34 (21 to 47)

Table 6 summarises the doses taken at treatment failure or last follow-up and indicates that reasonable dose ranges were tried before deciding that failure had occurred. The competing risks analysis shows that levetiracetam treatment was significantly more likely than lamotrigine treatment to fail due to ARs (HR 0.53, 95% CI 0.35 to 0.79) (see *Figure 7*), but not ISC (HR 0.67, 95% CI 0.45 to 1.01) (*Figure 8*). Similarly, zonisamide was significantly more likely to fail than lamotrigine due to ARs (HR 0.37, 95% CI 0.25 to 0.55), but not ISC (HR 0.76, 95% CI 0.50 to 1.15) (*Figure 9*).

Safety

Data were recorded on ARs for the SANAD II trial, which were defined as AEs judged by the treating clinicians to be possibly, probably or definitely caused by anti-seizure medication. *Table 7* provides an ITT (by treatment policy) summary of ARs according to the MedDRA System Organ Classification. Summaries by MedDRA-preferred term are presented in *Appendix 3*, *Table 33*.

There were 251 ARs experienced by 108 (33%) participants starting treatment with lamotrigine, 328 ARs experienced by 144 (44%) participants starting treatment with levetiracetam and 351 ARs in 146 (45%) participants starting treatment with zonisamide. The main difference in adverse effect profiles was in the prevalence of psychiatric symptoms, which were reported in 13.1% of those starting on lamotrigine, 29.7% of those starting on levetiracetam and 22.5% of those starting on zonisamide.

Seven events in two participants starting on lamotrigine were classified as a SAR, compared with one event in those starting on levetiracetam and four in those starting on zonisamide; there were no suspected unexpected serious adverse reactions (SUSARs) (see *Appendix 3*, *Table 34*). There were 37 deaths during the trial: 15 (four likely to be seizure related) in participants starting on lamotrigine, 12 (two likely to be seizure related) in those starting on levetiracetam and 10 (two likely to be seizure related) in those starting on zonisamide (see *Appendix 3*, *Table 35*).

There were 11 pregnancies in 11 women starting treatment with lamotrigine (10 with normal postnatal examination and one with minor malformations), six pregnancies in five women starting on levetiracetam (five with normal postnatal examination and one termination), and 17 pregnancies in 14 women starting treatment with zonisamide [eight with normal postnatal examination, eight miscarriages (in five women) and one termination] (see *Appendix 3*, *Table 36*).

TABLE 6 Doses taken at treatment withdrawal or last follow-up (those aged ≥ 12 years): lamotrigine vs. levetiracetam vs. zonisamide for focal epilepsy

Reason for withdrawal	Lamotrigine group	Levetiracetam group	Zonisamide group
Inadequate seizure control	*n* = 14	*n* = 16	*n* = 25
First follow-up/missing[a]	First follow-up = 1	First follow-up = 1, missing = 1	First follow-up = 1
Mean (SD) (mg)	267 (152)	2214 (955)	277 (136)
Range (mg)	75–500	500–3500	100–550
Unacceptable ARs	*n* = 34	*n* = 63	*n* = 77
First follow-up/missing	First follow-up = 16	First follow-up = 18	First follow-up = 20, missing = 3
Mean (SD) (mg)	171 (69)	1089 (473)	205 (101)
Range (mg)	50–300	10–2500	25–500
Other reason for withdrawal	*n* = 17	*n* = 17	*n* = 28
First follow-up/missing	First follow-up = 6	First follow-up = 8	First follow-up = 9, missing = 1
Mean (SD) (mg)	164 (94)	1188 (667)	242 (83)
Range (mg)	75–400	500–3000	150–400
Remission of seizures	*n* = 7	*n* = 7	*n* = 10
First follow-up/missing	0	First follow-up = 1	First follow-up = 1
Mean (SD) (mg)	183 (149)	1029 (221)	200 (61)
Range (mg)	50–500	800–1500	100–250
Still on randomised drug	*n* = 238	*n* = 188	*n* = 149
Missing	Missing = 11	Missing = 10	Missing = 17
Mean (SD) (mg)	222 (116)	1440 (726)	247 (112)
Range (mg)	50–700	250–4000	25–600

a If a drug was withdrawn at or before a patient's first follow-up, no information on the final dose was collected. 'First follow-up' denotes these patients; 'missing' denotes other patients with missing dose information.

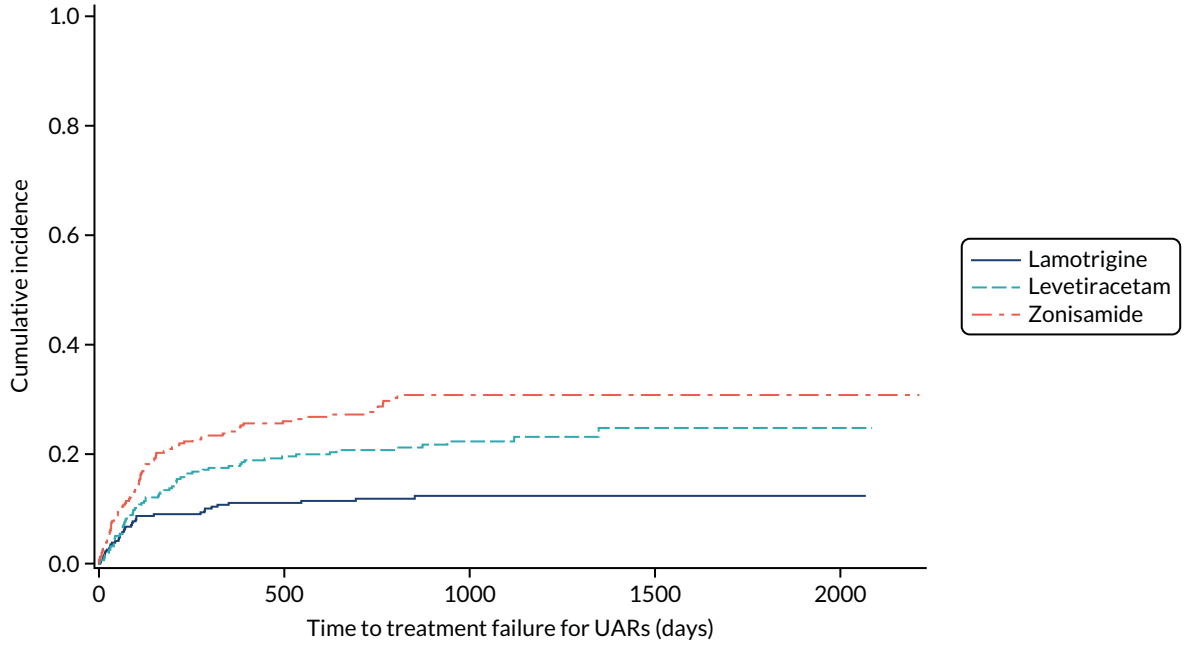

FIGURE 8 Cumulative incidence of treatment failure because of UARs from competing risks analysis: lamotrigine vs. levetiracetam vs. zonisamide for focal epilepsy.

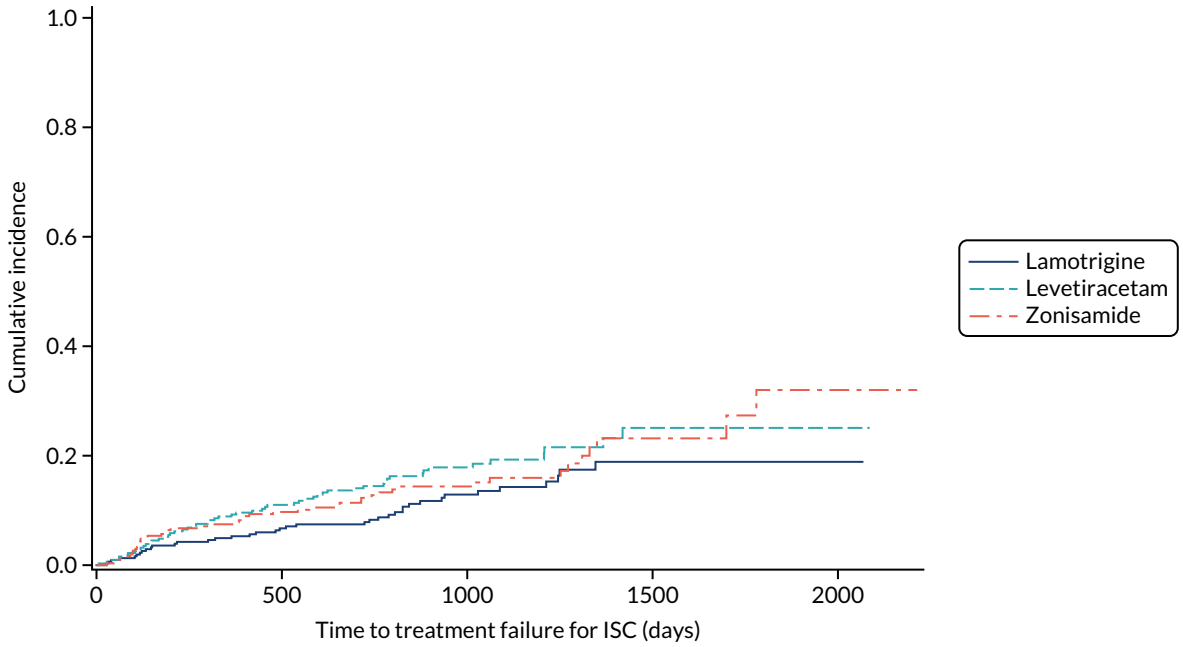

FIGURE 9 Cumulative incidence of treatment failure because of ISC from competing risks analysis: lamotrigine vs. levetiracetam vs. zonisamide for focal epilepsy.

TABLE 7 Adverse reactions by System Organ Classification

Event MedDRA System Organ Classification	Number of events			Number of patients (%)		
	Lamotrigine group	Levetiracetam group	Zonisamide group	Lamotrigine group (*N* = 328)	Levetiracetam group (*N* = 330)	Zonisamide group (*N* = 324)
Psychiatric disorders	58	147	103	43 (13.1)	98 (29.7)	73 (22.5)
Nervous system disorders	88	81	85	53 (16.2)	55 (16.7)	60 (18.5)
General disorders and administration site conditions[a]	23	37	44	17 (5.2)	32 (9.7)	39 (12.0)
Gastrointestinal disorders	30	29	35	25 (7.6)	22 (6.7)	26 (8.0)
Skin and subcutaneous tissue disorders	29	14	28	24 (7.3)	12 (3.6)	21 (6.5)
Investigations	6	11	16	6 (1.8)	11 (3.3)	16 (4.9)
Metabolism and nutrition disorders	4	2	17	3 (0.9)	2 (0.6)	16 (4.9)
Musculoskeletal and connective tissue disorders	5	1	8	5 (1.5)	1 (0.3)	7 (2.2)
Eye disorders	1	1	5	1 (0.3)	1 (0.3)	5 (1.5)
Renal and urinary disorders	1	0	6	1 (0.3)	0	5 (1.5)
Cardiac disorders	2	2	1	2 (0.6)	2 (0.6)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	1	1	2	1 (0.3)	1 (0.3)	2 (0.6)

continued

TABLE 7 Adverse reactions by System Organ Classification (*continued*)

Event MedDRA System Organ Classification	Number of events			Number of patients (%)		
	Lamotrigine group	Levetiracetam group	Zonisamide group	Lamotrigine group (*N* = 328)	Levetiracetam group (*N* = 330)	Zonisamide group (*N* = 324)
Injury, poisoning and procedural complications	2	0	0	2 (0.6)	0 (0.0)	0 (0.0)
Ear and labyrinth disorders	0	1	0	0 (0.0)	1 (0.3)	0 (0.0)
Endocrine disorders	0	1	0	0 (0.0)	1 (0.3)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	0	0	1	0 (0.0)	0 (0.0)	1 (0.3)
Vascular disorders	1	0	0	1 (0.3)	0 (0.0)	0 (0.0)
Total number of events and patients with at least one AR	251	328	351	108 (32.9)	144 (43.6)	146 (45.1)

a A total of 85% of ARs in this System Organ Classification were 'fatigue'.

Quality of life

A total of 493 (49.8%) participants returned QoL questionnaires at baseline and at least one other time point during follow-up. A comparison of those who did and did not return questionnaires showed a similar proportion of male and females, and a similar proportion of those with learning disabilities and neurological deficits to those without, but non-responders were slightly younger (*Table 8*).

TABLE 8 Comparison of the characteristics of those who did and those who did not return QoL questionnaires

Characteristic	No return	Return	Total
Age (years) (*n*)	497	493	990
Mean (SD)	34.2 (18.6)	44.5 (22.3)	39.3 (21.2)
Median (IQR)	32.2 (20.2–45.1)	44.9 (24.8–64.2)	37.7 (22.6–54.5)
Range	5.0–88.8	5.0–91.9	5.0–91.9
Missing	0	0	0
Gender (*n*)	497	493	990
Male, *n* (%)	288 (57.9)	273 (55.4)	561 (56.7)
Female, *n* (%)	209 (42.1)	220 (44.6)	429 (43.3)
Learning disability (*n*)	497	493	990
Yes, *n* (%)	28 (5.6)	17 (3.4)	45 (4.5)
No, *n* (%)	469 (94.4)	476 (96.6)	945 (95.5)
Neurological deficit (*n*)	497	493	990
Yes, *n* (%)	28 (5.6)	16 (3.2)	44 (4.4)
No, *n* (%)	469 (94.4)	477 (96.8)	946 (95.6)

TABLE 8 Comparison of the characteristics of those who did and those who did not return QoL questionnaires (*continued*)

Characteristic	No return	Return	Total
Previous or current neurological disorder, *n* (%)			
Stroke/cerebrovascular	21 (4.2)	26 (5.3)	47 (4.7)
Cerebral haemorrhage	10 (2.0)	4 (0.8)	14 (1.4)
Intracranial surgery	12 (2.4)	8 (1.6)	20 (2.0)
Patients with head injury and post-traumatic amnesia for > 24 hours or a compound depressed fracture	10 (2.0)	8 (1.6)	18 (1.8)
Meningitis/encephalitis	9 (1.8)	8 (1.6)	17 (1.7)
Cortical dysplasia/developmental anomaly	4 (0.8)	0 (0.0)	4 (0.4)
Other	29 (5.8)	40 (8.1)	69 (7.0)
History, *n* (%)			
Febrile convulsions	27 (5.4)	17 (3.4)	44 (4.4)
Any other acute symptomatic seizures	10 (2.0)	9 (1.8)	19 (1.9)
Family history of epilepsy in primary relatives	71 (14.3)	36 (7.3)	107 (10.8)

The return group includes those who were included in any longitudinal analyses, that is those who returned the questionnaire at baseline and at least one other time point (child, parent or adult).

Overall, lamotrigine was associated with a better profile on self-reported measures than levetiracetam or zonisamide. A comparison of the treatment effects in adults (*Table 9*) revealed negative treatment effects for levetiracetam when compared with lamotrigine for patient-reported anxiety, depression stigma, epilepsy impact and overall QoL. Compared with lamotrigine, zonisamide had a negative treatment effect for depression, epilepsy impact and overall QoL. A comparison of the treatment effects in children is summarised in *Table 10*. Owing to the small sample size, it is not possible to make any reliable inference about QoL effects.

TABLE 9 Results of longitudinal QoL analysis using mixed models: adults

QoL variable	Number of patients included in analysis	Treatment effect estimate (lamotrigine vs. levetiracetam)[a] (95% CI)	*p*-value	Treatment effect estimate (lamotrigine vs. zonisamide)[a] (95% CI)	*p*-value
AEs profile	405	−1.39 (−3.14 to 0.36)	0.118	−0.89 (−2.67 to 0.89)	0.327
Anxiety	406	−1.33 (−2.03 to −0.64)	< 0.001	−0.22 (−0.93 to 0.49)	0.544
Depression	406	−1.20 (−1.83 to −0.56)	< 0.001	−0.80 (−1.45 to −0.15)	0.015
Mastery	364	0.36 (−0.20 to 0.91)	0.206	0.32 (−0.25 to 0.89	0.276
Stigma	365	−0.50 (−0.96 to −0.04)	0.032	0.01 (−0.46 to 0.48)	0.962
Impact	362	1.87 (0.73 to 3.00)	0.001	1.82 (0.65 to 2.99)	0.002
Overall QoL	358	−0.52 (−0.77 to −0.26)	< 0.001	−0.41 (−0.67 to −0.15)	0.002

a Negative treatment effect estimates favour lamotrigine, with the exception of mastery and impact, where positive estimates favour lamotrigine.

TABLE 10 Results of longitudinal QoL analysis using mixed models: children

QoL variable	Number of patients included in analysis	Treatment effect estimate (lamotrigine vs. levetiracetam)[a] (95% CI)	*p*-value	Treatment effect estimate (lamotrigine vs. zonisamide)[a] (95% CI)	*p*-value
Self-reported					
Attitude to epilepsy	32	−1.40 (−17.38 to 14.58)	0.860	−9.46 (−23.79 to 4.86)	0.189
QoL physical	31	−0.89 (−17.27 to 15.50)	0.913	−1.01 (−16.10 to 14.08)	0.892
QoL emotional	31	−8.01 (−19.99 to 3.97)	0.184	−6.31 (−17.26 to 4.65)	0.251
QoL self-esteem	30	−9.54 (−25.85 to 6.77)	0.243	4.97 (−10.16 to 20.09)	0.510
QoL social	31	−1.86 (−12.87 to 9.15)	0.734	1.87 (−8.56 to 12.29)	0.718
QoL family	31	−13.82 (−29.44 to 1.80)	0.081	−7.44 (−21.84 to 6.96)	0.302
QoL school	30	−18.75 (−32.88 to −4.62)	0.011	−12.43 (−25.35 to 0.50)	0.059
Impact of epilepsy	7	1.82 (−27.06 to 30.70)	0.888	−4.81 (−27.58 to 17.95)	0.639
Parent proxy reported					
QoL physical	62	−4.22 (−13.93 to 5.48)	0.391	−6.10 (−15.49 to 3.28)	0.201
QoL emotional	61	0.10 (−9.09 to 9.29)	0.983	0.34 (−8.32 to 9.00)	0.939
QoL self-esteem	60	−5.44 (−13.58 to 2.70)	0.189	−2.39 (−10.15 to 5.37)	0.544
QoL social	60	−9.45 (−18.06 to −0.83)	0.032	−5.02 (−13.11 to 3.08)	0.222
QoL family	61	1.28 (−7.17 to 9.73)	0.765	1.36 (−6.62 to 9.34)	0.736
QoL school	61	−8.53 (−17.59 to 0.52)	0.065	−5.17 (−13.79 to 3.44)	0.237

a Positive treatment effect estimates favour lamotrigine.

Chapter 4 Focal epilepsy results: economic

Data completeness

The HES data were available for a total of 772 participants, relating to 266 participants randomised to start treatment with lamotrigine, 261 participants randomised to start treatment with levetiracetam and 245 participants randomised to start treatment with zonisamide. A breakdown of missing data by treatment group and outcome is provided in *Appendix 4*, *Table 48*.

A total of 789 participants completed at least one self-report questionnaire (completing the resource use, EQ-5D or both sections); 621 participants completed two or more questionnaires. In total, questionnaires were available for 3039 participant time points (once child and proxy questionnaires had been resolved).

Questionnaires returned after the change in protocol were assigned to their nearest time point for presentation purposes. Self-report resource use data were available for 550 participants at 3 months, 527 participants at 6 months, 465 participants at 12 months and 398 participants at 24 months. Resource use data were also available from 496 questionnaires returned at the later time points (36, 48 and 60 months).

Utility data (EQ-5D) were available for 616 participants at baseline; data were interpolated to 12 months for 422 participants and to 24 months for 319 participants. These are lower than the figures reported in *Appendix 4*, *Table 48*, because the 12- and 24-month questionnaires were dated less than 365 and 730 days post randomisation, respectively. For the NEWQOL-6D, fewer utility data were available because of a large number of partially completed questionnaires.

A total of 50 data sets were imputed, based on the largest fraction of missing information (0.7) and accepting < 1% reduction in power compared with 100 imputations. For the bootstrapped results, this was reduced to 10 for efficiency purposes, accepting a higher reduction in power to achieve an acceptable computation time.[64] Owing to the level of missingness, models containing the NEWQOL-6D were non-convergent; hence only complete-case results are presented for the NEWQOL-6D.

Resource use and costs

Table 11 presents the observed mean disaggregated resource use based on the self-report questionnaires. *Table 12* presents the most common admitted patient care episodes, outpatient and A&E-related HRGs, and costs observed during the trial period. During the 24-month follow-up period, 339 unique HRGs were recorded in admitted patient care, including 262 in outpatients and 35 in A&E.

Based on the imputed data, the majority of costs relate to secondary care, in particular admitted patient care and outpatient clinic attendance (*Table 13*). Comparing across treatment groups, zonisamide has higher secondary care costs and medicines costs than lamotrigine or levetiracetam. The total (unadjusted) costs were £5409 (97.5% CR £4584 to £6658) for participants randomised to start treatment with zonisamide, compared with £5074 (97.5% CR £4433 to £6049) for those

TABLE 11 Observed resource use based on self-report questionnaire (24-month time horizon)

Resource	Mean [range] (number of participants)											
	3-month time point			6-month time point			12-month time point			24-month time point		
	Lamotrigine group	Levetiracetam group	Zonisamide group	Lamotrigine group	Levetiracetam group	Zonisamide group	Lamotrigine group	Levetiracetam group	Zonisamide group	Lamotrigine group	Levetiracetam group	Zonisamide group
Questionnaires returned (*n*)	179	183	182	172	170	173	150	147	151	126	124	122
Primary care												
GP consultation at GP surgery	1.02 [0–8] (90)	1.13 [0–13] (88)	0.98 [0–10] (92)	0.67 [0–5] (63)	0.87 [0–10] (72)	0.89 [0–12] (71)	0.76 [0–14] (65)	1.01 [0–12] (67)	1.10 [0–8] (76)	0.83 [0–9] (52)	1.09 [0–10] (56)	1.01 [0–20] (52)
Nurse consultation at GP surgery	0.58 [0–11] (46)	0.50 [0–10] (42)	0.46 [0–10] (47)	0.42 [0–12] (45)	0.38 [0–6] (35)	0.56 [0–24] (42)	0.63 [0–12] (48)	0.71 [0–10] (51)	0.73 [0–8] (52)	0.83 [0–12] (51)	0.85 [0–8] (47)	0.74 [0–16] (41)
GP home visit	0.01 [0–1] (1)	0.04 [0–6] (3)	0.05 [0–5] (5)	0.02 [0–2] (2)	0.04 [0–2] (5)	0.02 [0–2] (3)	0	0.02 [0–2] (2)	0.01 [0–1] (1)	0.02 [0–2] (1)	0.08 [0–6] (3)	0.02 [0–1] (3)
Nurse home visit	0.10 [0–2] (14)	0.13 [0–6] (10)	0.05 [0–6] (4)	0.03 [0–1] (5)	0.37 [0–24] (11)	0.05 [0–12] (9)	0.01 [0–1] (1)	0.68 [0–95] (5)	0.01 [0–1] (1)	0.01 [0–1] (1)	0.19 [0–12] (10)	0.05 [0–2] (4)
Community care												
Health visitor	0.01 [0–1] (2)	0.06 [0–6] (4)	0.04 [0–3] (4)	0.01 [0–1] (1)	0.06 [0–5] (3)	0.02 [0–3] (1)	0.01 [0–1] (1)	0	0.01 [0–2] (1)	0.03 [0–4] (1)	0.04 [0–3] (3)	0.02 [0–2] (1)
Social worker	0.08 [0–7] (4)	0.04 [0–6] (3)	0.02 [0–2] (2)	0.06 [0–4] (3)	0.06 [0–6] (4)	0.03 [0–3] (3)	0.14 [0–20] (2)	0.07 [0–5] (4)	0.05 [0–4] (4)	0.02 [0–2] (2)	0.06 [0–4] (3)	0.06 [0–3] (4)
Occupational therapist	0.09 [0–4] (9)	0.15 [0–6] (14)	0.09 [0–4] (9)	0.05 [0–3] (5)	0.10 [0–6] (7)	0.03 [0–2] (5)	0.17 [0–20] (5)	0.07 [0–3] (7)	0.03 [0–2] (3)	0.02 [0–2] (1)	0.29 [0–27] (5)	0.05 [0–5] (2)
Psychologist	0.07 [0–4] (8)	0.16 [0–8] (10)	0.09 [0–5] (7)	0.06 [0–3] (7)	0.20 [0–18] (10)	0.06 [0–2] (8)	0.03 [0–2] (4)	0.14 [0–11] (5)	0.07 [0–2] (7)	0.07 [0–3] (5)	0.21 [0–6] (8)	0.25 [0–7] (9)
Counsellor	0.02 [0–2] (2)	0.10 [0–6] (4)	0.18 [0–13] (6)	0.07 [0–6] (3)	0.20 [0–8] (7)	0.29 [0–12] (11)	0.09 [0–9] (4)	0.22 [0–12] (7)	0.15 [0–12] (5)	0.06 [0–6] (3)	0.21 [0–16] (8)	0.22 [0–12] (5)
Physiotherapist	0.13 [0–6] (7)	0.16 [0–6] (10)	0.14 [0–6] (9)	0.09 [0–12] (4)	0.09 [0–4] (7)	0.13 [0–10] (7)	0.09 [0–7] (5)	0.32 [0–10] (11)	0.16 [0–12] (6)	0.13 [0–6] (6)	0.41 [0–27] (9)	22 [0–10] (7)
Secondary care												
Doctor at hospital	0.55 [0–3] (74)	0.79 [0–6] (86)	0.70 [0–6] (83)	0.68 [0–3] (86)	1.05 [0–61] (85)	0.79 [0–6] (92)	0.61 [0–4] (64)	0.63 [0–8] (56)	0.64 [0–5] (72)	0.53 [0–6] (49)	0.60 [0–7] (51)	0.61 [0–8] (44)
Nurse at hospital	0.47 [0–4] (66)	0.59 [0–6] (79)	0.59 [0–6] (77)	0.53 [0–16] (60)	0.46 [0–4] (62)	0.57 [0–6] (72)	0.47 [0–5] (53)	0.68 [0–13] (55)	0.53 [0–20] (45)	0.31 [0–5] (31)	0.41 [0–6] (38)	0.56 [0–10] (42)
Hospital overnight	0.28 [0–18] (12)	0.16 [0–6] (13)	0.15 [0–7] (15)	0.09 [0–7] (8)	0.09 [0–5] (6)	0.12 [0–6] (10)	0.24 [0–16] (6)	0.52 [0–46] (7)	0.24 [0–10] (10)	0.09 [0–4] (6)	0.84 [0–77] (9)	0.39 [0–28] (9)
Ambulance	0.18 [0–7] (21)	0.25 [0–7] (22)	0.17 [0–4] (19)	0.07 [0–2] (11)	0.14 [0–6] (13)	0.11 [0–3] (17)	0.08 [0–3] (9)	0.08 [0–2] (8)	0.15 [0–5] (14)	0.13 [0–2] (13)	0.10 [0–3] (9)	0.18 [0–5] (10)
A&E visit	0.27 [0–7] (28)	0.30 [0–5] (31)	0.23 [0–4] (24)	0.15 [0–2] (22)	0.21 [0–4] (21)	0.21 [0–9] (25)	0.27 [0–8] (24)	0.30 [0–15] (18)	0.23 [0–6] (23)	0.20 [0–3] (19)	0.29 [0–4] (21)	0.24 [0–5] (20)
Blood test	0.58 [0–11] (58)	0.36 [0–4] (51)	0.46 [0–24] (44)	0.34 [0–12] (42)	0.70 [0–59] (43)	0.46 [0–10] (44)	0.60 [0–16] (45)	0.48 [0–10] (41)	0.50 [0–7] (47)	0.73 [0–12] (47)	0.63 [0–7] (42)	0.52 [0–5] (40)
Urine test	0.14 [0–4] (20)	0.13 [0–3] (20)	0.22 [0–14] (23)	0.12 [0–2] (18)	0.29 [0–28] (18)	0.18 [0–3] (24)	0.16 [0–3] (18)	0.13 [0–2] (14)	0.07 [0–2] (9)	0.15 [0–3] (16)	0.15 [0–2] (14)	0.28 [0–9] (17)

Resource	Mean [range] (number of participants)											
	3-month time point			6-month time point			12-month time point			24-month time point		
	Lamotrigine group	Levetiracetam group	Zonisamide group	Lamotrigine group	Levetiracetam group	Zonisamide group	Lamotrigine group	Levetiracetam group	Zonisamide group	Lamotrigine group	Levetiracetam group	Zonisamide group
Ultrasound	0.09 [0–2] (16)	0.09 [0–3] (13)	0.09 [0–3] (13)	0.06 [0–2] (9)	0.05 [0–3] (7)	0.13 [0–2] (18)	0.07 [0–1] (9)	0.05 [0–4] (5)	0.08 [0–2] (10)	0.04 [0–2] (4)	0.07 [0–2] (8)	0.14 [0–4] (12)
Radiography	0.13 [0–6] (10)	0.10 [0–3] (13)	0.15 [0–8] (16)	0.08 [0–3] (10)	0.11 [0–2] (15)	0.16 [0–4] (20)	0.21 [0–3] (25)	0.08 [0–3] (8)	0.09 [0–2] 10	0.19 [0–6] (16)	0.16 [0–5] (14)	0.16 [0–3] (15)
CT scan	0.07 [0–2] (11)	0.08 [0–2] (14)	0.08 [0–2] (14)	0.03 [0–1] (6)	0.04 [0–1] (7)	0.04 [0–1] (7)	0.05 [0–2] (7)	0.03 [0–2] (3)	0.01 [0–1] (2)	0.02 [0–1] (2)	0.02 [0–1] (3)	0.01 [0–1] (1)
MRI scan	0.21 [0–2] (36)	0.21 [0–2] (37)	0.24 [0–2] (41)	0.06 [0–2] (10)	0.06 [0–1] (11)	0.09 [0–2] (15)	0.07 [0–2] (9)	0.01 [0–1] (1)	0.05 [0–1] (7)	0.02 [0–1] (2)	0.02 [0–1] (2)	0.02 [0–1] (3)
EEG	0.21 [0–4] (33)	0.15 [0–2] (26)	0.18 [0–2] (32)	0.04 [0–1] (7)	0.05 [0–1] (8)	0.03 [0–1] (6)	0.03 [0–1] (4)	0.01 [0–1] (2)	0.04 [0–2] (5)	0.01 [0–1] (1)	0.01 [0–1] (1)	0.01 [0–1] (1)
Other[a]	0.11 [0–2] (18)	0.12 [0–3] (19)	0.16 [0–7] (19)	0.09 [0–2] (12)	0.12 [0–2] (19)	0.35 [0–18] (18)	0.09 [0–2] (11)	0.07 [0–1] (10)	0.10 [0–2] (14)	0.42 [0–28] (14)	0.17 [0–10] (10)	0.20 [0–3] (18)

CAMHS, Child and Adolescent Mental Health Services; ECG, electrocardiography; FESS, functional endoscopic sinus surgery; MMR, measles, mumps and rubella vaccine; MRSA, meticillin-resistant *Staphylococcus aureus*; PET, positron emission tomography; SENCO, special educational needs co-ordinator.

a Refers to:

- Primary care: GP out of hours, telephone consultation (GP), MMR, repeat prescription, saliva test.
- Community care: dentist, orthodontist, school nurse, SENCO, speech therapist, support worker, psychiatrist, midwife, CAMHS, optician, NHS glasses, cervical smear, podiatrist, podiatrist minor surgery, dietitian, NHS direct, hearing test, mammogram.
- Outpatients: anticoagulant service, long-term EEG monitor, ECG, sleep apnoea test, endoscopy, cystoscopy, contrast fluoroscopy, grommets, tooth extraction, cerebral angiography, audiology, PET, nasal polypectomy, radiofrequency treatment, colonoscopy, minor skin procedures, field exercise test, FESS operation, dual X-ray absorptiometry, video telemetry, spinal fluid test, diabetic retinopathy screen, percutaneous biopsy, rib fracture, liver biopsy, radiotherapy, hand fracture, arm fracture, MRSA swabs, prostate biopsy, biopsy (nose, external), cardiac catheterisation, peak flow test, minor dental procedures.
- Admitted patient care: hernia operation, pelvis fracture, implantation of loop recorder, removal of loop recorder, vaginal tape operation, overnight sleep study, triple heart bypass, foot operation, pacemaker fitted, cholecystectomy, bursa excision, hysterectomy, knee replacement, cyst removal.
- A&E: see and treat (no convey), walk-in centre.

TABLE 12 Hospital attendances for the most frequent HRG codes for the 24-month trial period

HRG code	Description			Attendances (*n*)[a] Lamotrigine group	Levetiracetam group	Zonisamide group	Total
Admitted patient care							
AA26H	Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head injury, with a CC score of 0–2			15	20	20	60
SC97Z	Same-day radiotherapy admission or attendance (excluding Brachytherapy)			20	0	20	40
AA26G	Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head injury, with a CC score of 3–5			[b]	[b]	[b]	25
SB97Z	Same-day chemotherapy admission or attendance			25	0	0	25
AA33C	Conventional EEG, EMG or nerve conduction studies, 19 years and over			[b]	[b]	[b]	20
PR02B	Paediatric epilepsy syndrome with a CC score of 1–5			[b]	[b]	[b]	20
AA80Z	Complex long-term EEG monitoring			[b]	[b]	[b]	15
PR02C	Paediatric epilepsy syndrome with a CC score of 0			[b]	[b]	[b]	15
WH50B	Procedure not carried out, for other or unspecified reasons			[b]	[b]	[b]	10
WH04E	Poisoning diagnosis without interventions, with a CC score of 0 or 1			[b]	[b]	[b]	10
Outpatients							
400	Neurology	WF01A	Non-admitted face-to-face attendance, follow-up	800	840	825	2465
400	Neurology	WF01B	Non-admitted face-to-face attendance, first	195	185	160	540
420	Paediatrics	WF01A	Non-admitted face-to-face attendance, follow-up	120	155	145	420
400	Neurology	N/A	N/A	65	80	80	220
110	Trauma and orthopaedics	WF01A	Non-admitted face-to-face attendance, follow-up	70	60	65	200
650	Physiotherapy	WF01A	Non-admitted face-to-face attendance, follow-up	30	55	50	135
421	Paediatric neurology	WF01A	Non-admitted face-to-face attendance, follow-up	50	45	22	120
223	Paediatric epilepsy	N/A	N/A	20	20	80	115
110	Trauma and orthopaedics	N/A	N/A	40	45	30	115
320	Cardiology	WF01A	Non-admitted face-to-face attendance, follow-up	30	40	35	105

TABLE 12 Hospital attendances for the most frequent HRG codes for the 24-month trial period (*continued*)

HRG code	Description			Attendances (*n*)[a]			
				Lamotrigine group	Levetiracetam group	Zonisamide group	Total
A&E							
N/A	N/A	ASS02	See and treat and convey	140	170	185	490
T01NA	Type 01 non-admitted	VB09Z	Emergency medicine, category 1 investigation with category 1–2 treatment	105	100	90	295
T01NA	Type 01 non-admitted	VB08Z	Emergency medicine, category 2 investigation with category 1 treatment	50	55	70	180
T01NA	Type 01 non-admitted	VB11Z	Emergency medicine, no investigation with no significant treatment	30	25	30	85
T01A	Type 01 admitted	VB09Z	Emergency medicine, category 1 investigation with category 1–2 treatment	25	30	25	75
T01A	Type 01 admitted	VB08Z	Emergency medicine, category 2 investigation with category 1 treatment	20	25	25	65
T01NA	Type 01 non-admitted	VB07Z	Emergency medicine, category 2 investigation with category 2 treatment	15	30	20	60
T04NA	Type 01 non-admitted	VB09Z	Emergency medicine, category 1 investigation with category 1–2 treatment	b	b	b	45
T01A	Type 01 admitted	VB04Z	Emergency medicine, category 2 investigation with category 4 treatment	15	15	15	45
T03NA	Type 01 non-admitted	VB09Z	Emergency medicine, category 1 investigation with category 1–2 treatment	b	b	b	35

CC, complication or comorbidity; EMG, electromyogram; N/A, not applicable.
a Rounded to nearest 5.
b Indicates < 10.

TABLE 13 Aggregated cost totals as per base case (imputed, discounted)

	Totals (discounted) (£) at 24 months, mean (95% CR)			Difference (£), mean (95% CR)		
Type of care	Lamotrigine group	Levetiracetam group	Zonisamide group	Levetiracetam – lamotrigine	Zonisamide – lamotrigine	Zonisamide – levetiracetam
Primary and community care	682 (551 to 1018)	1303 (981 to 2009)	1013 (786 to 1631)	622 (148 to 1274)	331 (–31 to 940)	–290 (–979 to 398)
Primary care	332 (284 to 423)	532 (416 to 724)	411 (347 to 567)	200 (59 to 391)	79 (–25 to 236)	–121 (–306 to 82)
Community care	350 (228 to 646)	771 (489 to 1381)	602 (374 to 1117)	422 (5 to 1028)	253 (–95 to 778)	–169 (–795 to 409)
Secondary care	3025 (2606 to 3628)	3263 (2853 to 3723)	3882 (3140 to 4670)	237 (–486 to 847)	857 (–69 to 1680)	619 (–215 to 1509)
Admitted patient care	1170 (855 to 1631)	1156 (869 to 1443)	1663 (1153 to 2246)	–15 (–560 to 400)	493 (–178 to 1127)	507 (–75 to 1207)
Outpatient care	1519 (1393 to 1664)	1705 (1552 to 1876)	1784 (1547 to 2050)	186 (–26 to 401)	266 (–17 to 564)	80 (–202 to 392)
A&E	336 (269 to 425)	402 (314 to 528)	434 (316 to 582)	66 (–64 to 199)	98 (–55 to 259)	32 (–153 to 220)
Medicines	356 (294 to 475)	508 (412 to 665)	515 (423 to 668)	151 (–10 to 304)	158 (15 to 316)	7 (–154 to 193)
Anti-seizure medication	125 (103 to 158)	248 (213 to 292)	269 (244 to 298)	123 (75 to 171)	144 (104 to 184)	21 (–24 to 68)
Concomitant medication	231 (175 to 348)	260 (172 to 403)	246 (161 to 390)	28 (–122 to 171)	14 (–126 to 168)	–14 (–165 to 162)
Total	4063 (3617 to 4842)	5074 (4433 to 6049)	5409 (4584 to 6658)	1011 (–36 to 2066)	1347 (266 to 2550)	336 (–926 to 1634)

randomised to levetiracetam and £4063 (97.5% CR £4842 to £6317) for those randomised to lamotrigine. The differences between the zonisamide and levetiracetam groups (£336, 97.5% CR −£926 to £1634) and between the levetiracetam and lamotrigine groups (£1011, 97.5% CR −£36 to £2066) were not statistically significant. However, the difference in cost between zonisamide and lamotrigine was significant (£1347, 97.5% CR £226 to £2550).

Based on imputed data, the mean baseline costs were £1215 (97.5% CR £1061 to £1375) in the zonisamide group, £1191 (97.5% CR £1035 to £1398) in the levetiracetam group and £1239 (97.5% CR £1036 to £1464) in the lamotrigine group. The base-case analysis that adjusted for baseline costs, age, gender and epilepsy type with centre as random effects yielded a mean 2-year total cost of £5400 (97.5% CR £4659 to £6770) in the zonisamide group, compared with £5104 (97.5% CR £4450 to £6141) in the levetiracetam group and £4042 (97.5% CR £3626 to £4983) in the lamotrigine group. The differences between the zonisamide and levetiracetam groups (£297, 97.5% CR −£900 to £1624) and between the levetiracetam and lamotrigine groups (£1062, 97.5% CR −£1174 to £2133) were not statistically significant. There was a significant difference of £1358 (97.5% CR £376 to £2563) between the zonisamide and lamotrigine groups.

Utilities and quality-adjusted life-years

The distributions of participants' responses to the EQ-5D-3L-Y and the NEWQOL-6D questionnaires by randomised treatment group are presented in *Appendix 4*, *Figures 27* and *28*. Based on imputed data, mean baseline utilities were 0.766 (97.5% CR 0.733 to 0.804) in the levetiracetam group, 0.800 (97.5% CR 0.760 to 0.830) in the zonisamide group and 0.779 (97.5% CR 0.751 to 0.818) in the lamotrigine group. In the base-case adjusted analysis, levetiracetam was associated with a QALY gain of 1.474 years (97.5% CR 1.393 to 1.523 years) over the 2-year time horizon, whereas zonisamide was associated with a QALY gain of 1.502 years (97.5% CR 1.418 to 1.566 years) and lamotrigine was associated with a QALY gain of 1.605 years (97.5% CR 1.547 to 1.651 years). This corresponds to a negative incremental QALY gain of −0.025 years (97.5% CR −0.058 to 0.129 years) between levetiracetam and zonisamide. The incremental QALY gains of −0.103 years (97.5% CR −0.201 to −0.015 years) between zonisamide and lamotrigine and −0.128 years (97.5% CR −0.219 to −0.065 years) between levetiracetam and lamotrigine were significant.

The QALYs based on the NEWQOL-6D were calculated for complete-case data only, over the 2-year time horizon. Levetiracetam was associated with adjusted QALY gains of 1.703 years (97.5% CR 1.678 to 1.727 years), compared with 1.712 years (97.5% CR 1.690 to 1.735 years) for zonisamide and 1.710 years (97.5% CR 1.687 to 1.733 years) for lamotrigine. Levetiracetam was, therefore, associated with a negative incremental QALY gain of −0.007 years (97.5% CR −0.035 to 0.019 years) when compared with zonisamide, and with a negative incremental QALY gain of −0.007 years (97.5% CR −0.035 to 0.019 years) when compared with lamotrigine. The incremental QALY gain between zonisamide and lamotrigine was 0.002 years (97.5% CR −0.021 to 0.025 years).

The distribution of responses to the EQ-VAS is shown in *Table 14*. The adjusted analysis based on the EQ-VAS resulted in a QALY gain of 1.398 years (97.5% CR 1.324 to 1.479 years) in the levetiracetam

TABLE 14 Responses to the EQ-VAS thermometer by version and intervention group

	Lamotrigine group		Levetiracetam group		Zonisamide group	
Time point	*n*	Mean (97.5% CI)	*n*	Mean (97.5% CI)	*n*	Mean (97.5% CI)
Baseline	188	0.712 (0.681 to 0.744)	187	0.707 (0.672 to 0.743)	190	0.751 (0.717 to 0.784)
12 months	127	0.767 (0.722 to 0.812)	124	0.706 (0.656 to 0.757)	130	0.712 (0.664 to 0.759)
24 months	106	0.752 (0.701 to 0.803)	106	0.715 (0.656 to 0.774)	109	0.726 (0.673 to 0.780)

group, 1.418 years (97.5% CR 1.351 to 1.456 years) in the zonisamide group and 1.431 years (97.5% CR 1.360 to 1.476 years) in the lamotrigine gorup. The negative incremental QALY gains of –0.020 years (97.5% CR –0.094 to 0.085 years) for levetiracetam compared with zonisamide, –0.013 years (97.5% CR –0.085 to 0.060 years) for zonisamide compared with lamotrigine and –0.033 years (97.5% CR –0.112 to 0.075 years) for levetiracetam compared with lamotrigine are consistent with the base-case EQ-5D.

Incremental analysis

Based on the point estimate mean costs and QALYs, both levetiracetam and zonisamide were more costly and less effective than lamotrigine, and were therefore dominated, meaning that they are not considered to be cost-effective. Zonisamide is associated with a negative INHB (–0.171, 97.5% CR –0.295 to –0.055) compared with lamotrigine, and levetiracetam is associated with a negative INHB compared with zonisamide (–0.010, 97.5% CR –0.142 to 0.112) at a cost-effectiveness threshold of £20,000 per QALY.

Sensitivity analyses

Table 15 presents the results of the sensitivity analyses, which are consistent with the base case for all analyses other than the NEWQOL-6D, where the NHB for levetiracetam is seen to be higher than for zonisamide at the £20,000 per QALY cost-effectiveness threshold. *Table 15* also presents the complete-case analysis in which levetiracetam is associated with lower costs than lamotrigine, but lamotrigine is still associated with the higher NHB.

The cost-effectiveness acceptability curve (*Figure 10*) indicates that the probability of levetiracetam being the most cost-effective treatment at a cost-effectiveness threshold of £20,000 per QALY is 0, and the probability of zonisamide being the most effective treatment is 0.001.

Subgroup analyses

The results of the subgroup analysis for adults are consistent with the base-case analysis for the whole population (*Table 16*). For children, however, lamotrigine is associated with the highest costs (£5076, 97.5% CR £3815 to £7219) compared with levetiracetam (£4972, 97.5% CR £3739 to £6840) and zonisamide (£4638, 97.5% CR £3826 to £6974). Levetiracetam is associated with a higher QALY gain than lamotrigine and, therefore, lamotrigine is dominated. Zonisamide has a lower cost and lower QALY gain than levetiracetam, but also a lower NHB at a cost-effectiveness threshold of £20,000 per QALY, and is therefore not cost-effective at that threshold.

TABLE 15 Results of sensitivity analyses. Anti-seizure medications ranked by cost-effectiveness, based on NHB at a cost-effectiveness threshold of £20,000 per QALY

Anti-seizure medication	Mean (97.5% CR)					
	Total cost (£)	QALYs	NHB at £20,000 per QALY	NHB at £30,000 per QALY	INHB at £20,000 per QALY	INHB at £30,000 per QALY
***Base case* (n = *990*)**						
Lamotrigine	4042 (3626 to 4983)	1.605 (1.547 to 1.651)	1.403 (1.319 to 1.458)	1.470 (1.399 to 1.520)		
Zonisamide	5400 (4659 to 6770)	1.502 (1.418 to 1.566)	1.232 (1.112 to 1.307)	1.322 (1.215 to 1.392)	−0.174 (−0.300 to −0.056)	−0.151 (−0.266 to −0.045)
Levetiracetam	5104 (4450 to 6141)	1.474 (1.393 to 1.523)	1.222 (1.110 to 1.283)	1.307 (1.204 to 1.361)	−0.011 (−0.146 to 0.114)	−0.016 (−0.139 to 0.091)
***0% discount rate (costs and QALYs) (base case 3.5%)* (n = *990*)**						
Lamotrigine	4108 (3682 to 5059)	1.633 (1.573 to 1.680)	1.428 (1.343 to 1.484)	1.496 (1.423 to 1.546)		
Zonisamide	5483 (4727 to 6872)	1.528 (1.442 to 1.592)	1.254 (1.131 to 1.330)	1.322 (1.236 to 1.416)	−0.168 (−0.291 to −0.055)	−0.146 (−0.258 to −0.044)
Levetiracetam	5189 (4517 to 6255)	1.502 (1.417 to 1.549)	1.243 (1.128 to 1.305)	1.307 (1.224 to 1.385)	−0.010 (−0.139 to 0.111)	−0.014 (−0.133 to 0.091)
***6% discount rate (costs and QALYs) (base case 3.5%)* (n = *990*)**						
Lamotrigine	3998 (3587 to 4935)	1.586 (1.529 to 1.632)	1.386 (1.303 to 1.440)	1.453 (1.382 to 1.501)		
Zonisamide	5344 (4613 to 6698)	1.485 (1.402 to 1.548)	1.218 (1.100 to 1.291)	1.307 (1.201 to 1.376)	−0.168 (−0.291 to −0.055)	−0.146 (−0.258 to −0.044)
Levetiracetam	5046 (4405 to 6066)	1.461 (1.378 to 1.505)	1.208 (1.097 to 1.268)	1.292 (1.191 to 1.346)	−0.010 (−0.139 to 0.111)	−0.014 (−0.133 to 0.089)
***Unadjusted (no covariates) (base-case adjusted)* (n = *990*)**						
Lamotrigine	4063 (3617 to 4842)	1.600 (1.524 to 1.649)	1.397 (1.301 to 1.450)	1.465 (1.374 to 1.515)		
Zonisamide	5409 (4584 to 6658)	1.521 (1.431 to 1.591)	1.251 (1.078 to 1.278)	1.341 (1.176 to 1.354)	−0.146 (−0.279 to −0.006)	−0.124 (−0.247 to 0.005)
Levetiracetam	5074 (4433 to 6049)	1.459 (1.362 to 1.517)	1.205 (1.129 to 1.339)	1.290 (1.233 to 1.421)	−0.045 (−0.195 to 0.095)	−0.051 (−0.183 to 0.076)
Complete-case data (cost*, n = *178; EQ-5D*, n = *225) (base-case imputed)						
Lamotrigine	3635 (2431 to 4828)	1.628 (1.576 to 1.684)	1.446 (1.367 to 1.537)	1.507 (1.440 to 1.583)		
Levetiracetam	3294 (2063 to 4504)	1.481 (1.418 to 1.545)	1.316 (1.234 to 1.401)	1.371 (1.299 to 1.444)	−0.131 (−0.244 to −0.024)	−0.136 (−0.233 to −0.045)
Zonisamide	4704 (3375 to 6255)	1.548 (1.483 to 1.601)	1.313 (1.200 to 1.405)	1.391 (1.296 to 1.466)	−0.003 (−0.146 to 0.112)	−0.020 (−0.094 to 0.109)

continued

TABLE 15 Results of sensitivity analyses. Anti-seizure medications ranked by cost-effectiveness, based on NHB at a cost-effectiveness threshold of £20,000 per QALY (*continued*)

Anti-seizure medication	Mean (97.5% CR)					
	Total cost (£)	QALYs	NHB at £20,000 per QALY	NHB at £30,000 per QALY	INHB at £20,000 per QALY	INHB at £30,000 per QALY
PP (n = 959) (base case all participants, ITT)						
Lamotrigine	4052 (3626 to 5023)	1.605 (1.546 to 1.650)	1.402 (1.315 to 1.456)	1.470 (1.397 to 1.519)		
Zonisamide	5480 (4702 to 6826)	1.503 (1.420 to 1.565)	1.229 (1.114 to 1.304)	1.320 (1.217 to 1.390)	−0.174 (−0.294 to −0.059)	−0.150 (−0.255 to −0.046)
Levetiracetam	5118 (4465 to 6185)	1.478 (1.394 to 1.523)	1.221 (1.401 to 1.280)	1.307 (1.202 to 1.361)	−0.007 (−0.137 to 0.111)	−0.013 (−0.131 to 0.088)
NEWQOL-6D (base-case EQ-5D) (costs as base case, NEWQOL-6D based on n = 132 complete cases)						
Lamotrigine	4042 (3626 to 4983)	1.710 (1.687 to 1.733)	1.508 (1.455 to 1.567)	1.575 (1.536 to 1.600)		
Levetiracetam	5104 (4450 to 6141)	1.703 (1.678 to 1.727)	1.448 (1.390 to 1.488)	1.533 (1.489 to 1.565)	−0.060 (−0.119 to −0.004)	−0.042 (−0.086 to −0.000)
Zonisamide	5400 (4659 to 6770)	1.712 (1.690 to 1.735)	1.442 (1.368 to 1.483)	1.532 (1.479 to 1.564)	−0.006 (−0.081 to 0.060)	−0.001 (−0.054 to 0.045)
EQ-VAS (base-case EQ-5D) (n = 990)						
Lamotrigine	4042 (3626 to 4983)	1.431 (1.360 to 1.476)	1.229 (1.127 to 1.281)	1.296 (1.207 to 1.346)		
Zonisamide	5400 (4659 to 6770)	1.418 (1.351 to 1.456)	1.148 (1.044 to 1.200)	1.238 (1.148 to 1.283)	−0.081 (−0.183 to 0.016)	−0.058 (−0.147 to 0.028)
Levetiracetam	5104 (4450 to 6141)	1.398 (1.324 to 1.479)	1.142 (1.042 to 1.223)	1.227 (1.138 to 1.308)	−0.006 (−0.102 to 0.121)	−0.011 (−0.093 to 0.105)
Treating blank responses in the questionnaire as missing (base case: as zero)						
Lamotrigine	4059 (3609 to 4901)	1.605 (1.547 to 1.651)	1.402 (1.329 to 1.449)	1.470 (1.403 to 1.515)		
Zonisamide	5532 (4716 to 6754)	1.502 (1.418 to 1.566)	1.226 (1.120 to 1.299)	1.318 (1.221 to 1.384)	−0.176 (−0.284 to −0.074)	−0.152 (−0.255 to −0.057)
Levetiracetam	5100 (4430 to 6235)	1.474 (1.393 to 1.523)	1.222 (1.120 to 1.275)	1.307 (1.216 to 1.355)	−0.003 (−0.127 to 0.105)	−0.010 (−0.120 to 0.086)

Unless stated, incremental values are relative to the row above.

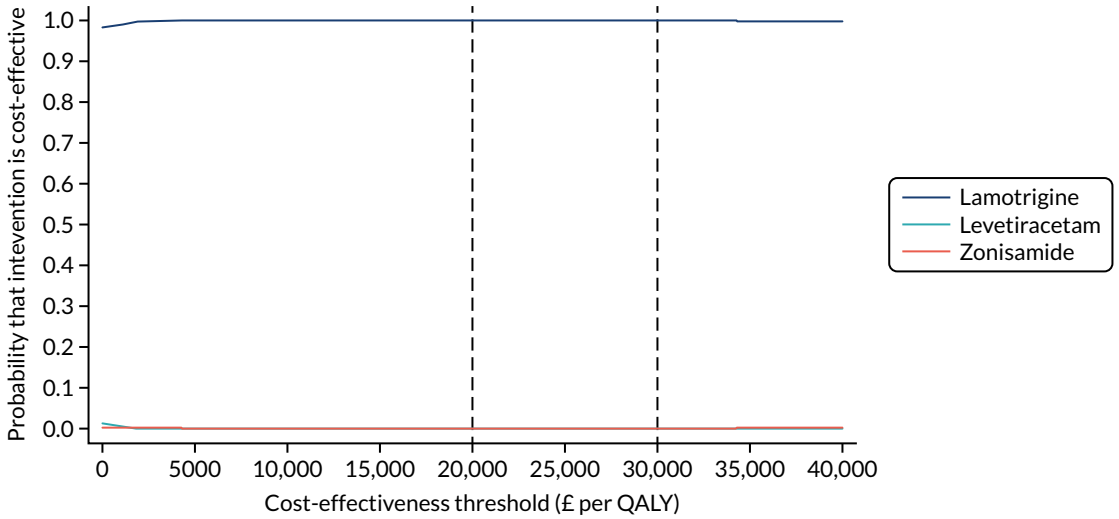

FIGURE 10 Cost-effectiveness acceptability curve. Dashed lines represent cost-effectiveness thresholds of £20,000 per QALY and £30,000 per QALY.

TABLE 16 Results of subgroup analysis. Anti-seizure medications ranked by cost-effectiveness, based on NHB at a cost-effectiveness threshold of £20,000 per QALY

Anti-seizure medication	Mean (97.5% CR)					
	Total cost (£)	QALYs	NHB at £20,000 per QALY	NHB at £30,000 per QALY	INHB at £20,000 per QALY	INHB at £30,000 per QALY
***Base case* (n = *990*)**						
Lamotrigine	4042 (3626 to 4983)	1.605 (1.547 to 1.651)	1.403 (1.319 to 1.458)	1.470 (1.399 to 1.520)		
Zonisamide	5400 (4659 to 6770)	1.502 (1.418 to 1.566)	1.232 (1.112 to 1.307)	1.322 (1.215 to 1.392)	−0.171 (−0.295 to −0.055)	−0.148 (−0.261 to −0.045)
Levetiracetam	5104 (4450 to 6141)	1.474 (1.393 to 1.523)	1.222 (1.110 to 1.283)	1.307 (1.204 to 1.361)	−0.010 (−0.142 to 0.112)	−0.015 (−0.136 to 0.089)
***Children aged < 16 years* (n = *155*)**						
Levetiracetam	4972 (3739 to 6840)	1.556 (1.397 to 1.618)	1.307 (1.097 to 1.394)	1.390 (1.207 to 1.463)		
Lamotrigine	5076 (3815 to 7219)	1.551 (1.432 to 1.638)	1.297 (1.107 to 1.412)	1.382 (1.221 to 1.481)	−0.010 (−0.171 to 0.191)	−0.009 (−0.148 to 0.173)
Zonisamide	4638 (3826 to 6974)	1.508 (1.381 to 1.610)	1.277 (1.068 to 1.390)	1.354 (1.176 to 1.460)	−0.020 (−0.242 to 0.175)	−0.028 (−0.214 to 0.143)
***Adults aged ≥ 16 years* (n = *835*)**						
Lamotrigine	3844 (3379 to 4478)	1.612 (1.554 to 1.661)	1.420 (1.346 to 1.475)	1.484 (1.417 to 1.536)		
Zonisamide	5509 (4610 to 6866)	1.508 (1.413 to 1.569)	1.227 (1.101 to 1.320)	1.319 (1.209 to 1.398)	−0.193 (−0.322 to −0.083)	−0.165 (−0.278 to −0.067)
Levetiracetam	5178 (4435 to 6223)	1.466 (1.381 to 1.518)	1.207 (1.095 to 1.280)	1.294 (1.193 to 1.359)	−0.020 (−0.158 to 0.112)	−0.025 (−0.149 to 0.090)

Unless stated, incremental values are relative to the row above.

Chapter 5 Focal epilepsy: discussion

For first-line treatment of focal epilepsy, zonisamide met our definition of non-inferiority for time to 12-month remission when compared with lamotrigine, but levetiracetam did not. No significant difference was found between lamotrigine and zonisamide in time to 24-month remission and time to first seizure. Both levetiracetam and zonisamide were significantly inferior to lamotrigine in terms of time to treatment failure.

It is important to highlight that the SANAD II trial was a pragmatic trial comparing the policies of initiating treatment with lamotrigine, levetiracetam or zonisamide, and that the primary analyses were on an ITT basis. This is particularly important when considering the outcomes of time to 12- and 24-month remission. The trial protocol recommended initial maintenance doses and titration rates, but, during follow-up, clinicians were able to make dose and drug changes as per usual clinical practice to maximise seizure control and minimise ARs. Therefore, it is reassuring to note that at 4 years the proportions achieving a 12-month remission were 82% (95% CI 77% to 88%) in those starting treatment with lamotrigine, 77% (95% CI 71% to 82%) in those starting treatment with levetiracetam and 84% (95% CI 78% to 90%) in those starting treatment with zonisamide.

Although the longer-term seizure outcomes are similar among the three treatment policies, levetiracetam and zonisamide are significantly more likely to fail than lamotrigine, resulting in treatment changes. The competing risks analysis shows that levetiracetam is more likely than lamotrigine to fail because of ARs (HR 0.53, 95% CI 0.35 to 0.79) and, although non-significant, the estimate also indicates a higher failure rate attributable to ISC (HR 0.67, 95% CI 0.45 to 1.01). Similarly, zonisamide is significantly more likely than lamotrigine to fail because of the ARs (HR 0.37, 95% CI 0.25 to 0.55) and, although non-significant, the estimate also indicates a higher failure rate attributable to ISC (HR 0.76, 95% CI 0.50 to 1.15). Treatment failures were taken into account in the PP analysis of time to 12-month remission, which took a competing risks approach and found lamotrigine to be superior to both levetiracetam (HR 1.32, 95% CI 1.05 to 1.66) and zonisamide (HR 1.37, 95% CI 1.08 to 1.73).

Initiating treatment with lamotrigine was associated with fewer ARs than initiating treatment with levetiracetam or zonisamide, and there were more psychiatric ARs in the groups starting on levetiracetam and zonisamide than in the group starting on lamotrigine. It is interesting to note that there were more pregnancies and miscarriages in the zonisamide group, but the numbers are too small to draw any conclusions.

The QoL analysis also found an overall better profile for lamotrigine than that for levetiracetam or zonisamide. Compared with lamotrigine, levetiracetam and zonisamide are associated with worse overall patient-reported QoL and depression. In addition, levetiracetam resulted in worse patient-reported anxiety, depression and stigma than lamotrigine or zonisamide.

The economic analysis indicated that neither levetiracetam nor zonisamide were cost-effective compared with lamotrigine, being both more costly and less effective and with lower NHBs over the 2-year time horizon of analysis. The mean total costs were £5400 (97.5% CR £4659 to £6770) for zonisamide and £5104 (97.5% CR £4450 to £6141) for levetiracetam, compared with £4042 (97.5% CR £3626 to £4983) for lamotrigine.

Levetiracetam and zonisamide were associated with lower QALY gains, at 1.474 years (97.5% CR 1.393 to 1.523 years) and 1.502 years (97.5% CR 1.418 to 1.566 years), respectively, than lamotrigine, at 1.605 years (97.5% CR 1.547 to 1.651 years).

Based on rank-ordering of NHBs, lamotrigine was highest at both the £20,000 and £30,000 per QALY thresholds of cost-effectiveness. This result was robust to a range of assumptions tested in sensitivity analyses, but although levetiracetam was the most cost-effective treatment in children, this subgroup analysis was limited by small numbers, and higher costs in the lamotrigine arm were principally attributable to a single participant who experienced an atypical medical journey.

As with the first SANAD trials,[9,16] we have demonstrated that the NHS in the UK can deliver longer-term pragmatic epilepsy trials, collecting data from neurology and paediatric services as well as from primary care. Given the duration of the study, the quantity of follow-up data collected was high; completeness of follow-up statistic 77.2% lamotrigine, 78.3% levetiracetam and 75.6% zonisamide for the primary outcome. Nonetheless, the SANAD II trial has a number of limitations. Data on the occurrence of seizures were collected using seizure diaries and reports at clinic visits. This is a limitation of almost all outpatient clinical trials in epilepsy, as there is no other practical method for ascertaining the occurrence of seizures. It is therefore possible that seizures were missed or not reported, although there is no reason to expect systematic under- or over-reporting of seizures in any of the randomised groups. The SANAD II trial was unblinded, which was the only feasible way to collect longer-term follow-up data when knowledge of first treatment is required to inform future treatment decisions. This may have influenced decisions about dose and treatment changes, thereby biasing results for time to treatment failure and seizure outcomes. Knowledge of treatment allocated may also have influenced the reporting of ARs, and this should be taken into consideration when interpreting, for example, the higher rate of psychiatric events in the levetiracetam and zonisamide groups. In addition, only 17.9% of those recruited were aged < 18 years. The most likely explanation for this lower than expected percentage was the lack of experience with zonisamide among paediatricians, which may have introduced a reluctance to recruit patients to the trial. Clearly, this will limit the applicability of the results to the management of children with focal epilepsy. It is possible that the maintenance doses chosen introduce a systematics bias, but the similar rates of time to first seizure rates provide assurance that appropriate initial maintenance doses were chosen, and mitigates against concerns that the slower titration rate required for lamotrigine might expose individuals to risk of early seizure recurrence.

It is also important to acknowledge that there are no RCT data to inform the choice of initial maintenance dose of lamotrigine, levetiracetam, zonisamide or most other anti-seizure medications. Slightly more males than females were recruited (57% vs. 43%), and in the SANAD I trial we found that men had a higher 12-month remission rate than women, although it remains unproven as to whether this is a true treatment effect or due to under-reporting of seizures by males.[7] There was also a low return rate for QoL questionnaires and, although the rates of return were not unusually low for postal questionnaires, this will have diminished our ability to identify differences in QoL.

The economic analysis was limited by the poor return of self-report questionnaires. However, for costs this was largely mitigated by the acquisition of HES data and the use of follow-up CRFs for the costs of anti-seizure medicines, which were the main cost drivers. Owing to the AUC methodology, QALYs could be calculated provided that two or more EQ-5D questionnaires had been returned. However, for the NEWQOL-6D there were insufficient data to complete imputation; hence, only complete-case results could be presented. An additional limitation was that there is no tariff currently available for the EQ-5D-3L-Y or proxy version of the EQ-5D-3L and, therefore, the adult tariff was used throughout for estimating utilities from EQ-5D profiles. This represents a weakness in many economic evaluations of interventions in paediatric populations,[75] although a valuation of children's EQ-5D-3L-Y health states should soon be available.[76] Furthermore, given the chronic nature of epilepsy, the 2-year time horizon is somewhat limited and the planned analysis over a 4-year time horizon could not be conducted because of the limitations of missing data.

These results should be interpreted in context with previous studies that have assessed the longer-term effectiveness of treatments for focal epilepsies. One limitation is that most RCTs that have compared anti-seizure medication monotherapies in epilepsy have been undertaken to meet regulatory requirements and have not assessed longer-term outcomes. For example, the European Medicines Agency recommends assessing 6-month seizure remission rates in head-to-head trials with a standard treatment,[77] whereas the Food and Drug Administration will not accept head-to-head non-inferiority trials because of concerns that interpretation as a finding of equivalence or non-inferiority could be due to treatments being similarly ineffective (assay sensitivity).[78]

The SANAD I trial identified lamotrigine as a first-line treatment as it was non-inferior to carbamazepine for time to 12-month remission and superior to carbamazepine, gabapentin, oxcarbazepine and topiramate for time to treatment failure.[9] Lamotrigine was subsequently recommended as a first-line treatment[8] and was chosen as the standard treatment for focal epilepsy in the SANAD II trial. An individual patient data network meta-analysis,[15] which included data from the SANAD I trial and combined direct and indirect comparisons, used carbamazepine as the standard treatment comparator for focal epilepsy. The results indicated that levetiracetam was inferior to carbamazepine for time to 12-month remission, but was not significantly different to gabapentin, lamotrigine, phenobarbital, phenytoin (Epanutin®, Upjohn UK Ltd), oxcarbazepine, valproate or zonisamide. For time to treatment failure, lamotrigine and levetiracetam were superior to carbamazepine, phenobarbital was inferior to carbamazepine, and no difference was found between carbamazepine and the other assessed treatments. Therefore, these findings suggest that the SANAD II trial provides much needed longer-term head-to-head data to better inform treatment policy and guidance.

The SANAD II results have important implications for clinical practice and research. Although levetiracetam and zonisamide are licensed for use as monotherapy in focal epilepsy in Europe and elsewhere, these results suggest that their use as first-line monotherapy may not be supported. This is most relevant to levetiracetam, which has become a commonly prescribed first-line anti-seizure medication, based on easy titration, perceived good efficacy and an assumed low rate of ARs. The SANAD II trial also provides evidence that the slower titration of lamotrigine is not associated with a shorter time to first subsequent seizure and that levetiracetam has a higher withdrawal rate due to ARs. Further studies are required to assess the clinical effectiveness and cost-effectiveness of other newer anti-seizure medications, such as lacosamide (Vimpat®, UCB Pharma Ltd), brivaracetam (Briviact®, UCB Pharma Ltd) and perampanel (Fycompa®, Eisai Co. Ltd), and the design of future studies should be debated given that the SANAD I and SANAD II trials provide historical control data.

Recommendations for research

1. A network meta-analysis making both direct and indirect comparisons is required of all available anti-seizure monotherapy trials to provide an overview of the entirety of current evidence regarding clinical effectiveness for focal epilepsy. This work is under way and funded by the National Institute for Health Research (NIHR) to inform the current NICE epilepsy guidelines update.[79]
2. An economic model is required, utilising the results of direct and indirect comparisons to estimate the comparative cost-effectiveness of currently available treatments for focal epilepsy.
3. Prognostic modelling of data from the SANAD I and SANAD II trials is required to explore subgroup effects and to better stratify patients for likely outcome at the time of initiating treatment for focal epilepsy.
4. Methodological work, utilising data from the SANAD I and SANAD II trials is required to inform the design of future trials assessing the clinical effectiveness and cost-effectiveness of anti-seizure medications in people with newly diagnosed focal epilepsy. This includes the possibility of designs using data from the SANAD I and SANAD II trials as historical controls.
5. Future trials are required to assess the clinical effectiveness and cost-effectiveness of other focal epilepsy treatments including lacosamide, brivaracetam, perampanel and clobazam.

In conclusion, the SANAD II results indicate that lamotrigine should remain a first-line standard treatment for focal epilepsy and that neither levetiracetam nor zonisamide should be used as routine first-line anti-seizure medications.

Chapter 6 Generalised and unclassified epilepsy: clinical results

Recruitment and baseline characteristics

The first participant was randomised on 30 April 2013 and the last participant was randomised on 2 August 2016 (see *Appendix 3*, *Figure 25*), after which every effort was made to follow the trial cohort for a further 2 years, and the last participant visit was on 13 January 2019. Sixty-nine UK centres recruited between 1 and 40 patients each, and randomised a total of 520 participants: 260 to start treatment with levetiracetam and 260 to start treatment with valproate (*Figure 11*). Baseline characteristics

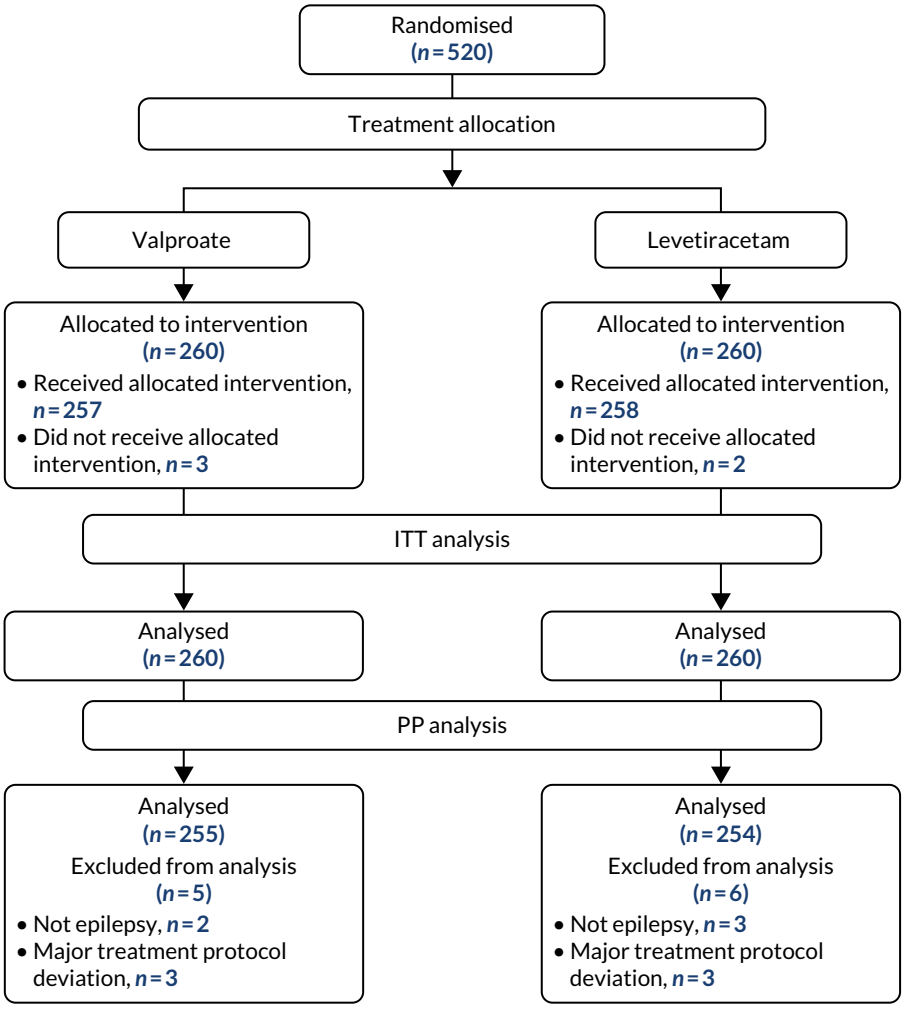

FIGURE 11 The CONSORT participant flow diagram: generalised and unclassified epilepsy trial.

were well balanced across treatment groups (*Table 17* and see *Appendix 3*, *Table 37*). The median age of participants was 13.9 years (IQR 8.9–19.7 years) with a predominance of males (64.8%), reflecting concern about randomising females to valproate. Approximately 10% of patients had a learning disability, 3.1% a neurological deficit and 19% had a first-degree relative with epilepsy. Approximately three-quarters of the participants had generalised epilepsy and in the remainder the type of epilepsy was unclassified. Of those with generalised epilepsy (397), 26.2% had childhood absence epilepsy, 9.1% juvenile absence epilepsy, 12.8% juvenile myoclonic epilepsy, 5.8% generalised epilepsy with tonic–clonic seizures on waking and 45.3% were classified as having 'idiopathic generalised epilepsy not specified'. Participants were randomised a median of 4 days (IQR 0–26 days) after their most recent seizure.

TABLE 17 Baseline characteristics

Characteristic	Valproate group	Levetiracetam group	Total
Number of participants	260	260	520
Age (years)			
Mean (SD)	17.1 (12.9)	16.9 (11.8)	17.0 (12.3)
Median (IQR)	13.6 (8.8–19.7)	14.1 (9.1–19.8)	13.9 (8.9–19.7)
Range	5.0–94.4	5.0–83.9	5.0–94.4
Age group (years), *n* (%)			
5–7	52 (20.0)	48 (18.5)	100 (19.2)
8–11	54 (20.8)	56 (21.5)	110 (21.2)
12–15	54 (20.8)	48 (18.5)	102 (19.6)
16–29	70 (26.9)	81 (31.2)	151 (29.0)
≥ 30	30 (11.5)	27 (10.4)	57 (11.0)
Gender, *n* (%)			
Male	167 (64.2)	170 (65.4)	337 (64.8)
History, *n* (%)			
Learning disability	22 (8.5)	29 (11.2)	51 (9.8)
Febrile convulsions	21 (8.1)	23 (8.8)	44 (8.5)
Acute symptomatic seizures	4 (1.5)	10 (3.8)	14 (2.7)
History of epilepsy in primary relatives	49 (18.8)	50 (19.2)	99 (19.0)
Neurological deficit	6 (2.3)	10 (3.8)	16 (3.1)
Previous or current neurological disorder, *n* (%)			
Stroke/cerebrovascular	0	0	0
Cerebral haemorrhage	0	2 (0.8)	2 (0.4)
Intracranial surgery	0	2 (0.8)	2 (0.4)
Head injury[a]	1 (0.4)	1 (0.4)	2 (0.4)
Meningitis/encephalitis	4 (1.5)	0	4 (0.8)
Cortical dysplasia/developmental anomaly	0	0	0
Other	11 (4.2)	13 (5.0)	24 (4.6)
Epilepsy type, *n* (%)			
Generalised	201 (77.3)	196 (75.4)	397 (76.3)
Unclassified	59 (22.7)	64 (24.6)	123 (23.7)

TABLE 17 Baseline characteristics (*continued*)

Characteristic	Valproate group	Levetiracetam group	Total
Epilepsy syndrome (generalised epilepsy only),[b] *n* (%)			
Childhood absence	52 (25.9)	52 (26.5)	104 (26.2)
Juvenile absence	22 (10.9)	14 (7.1)	36 (9.1)
Juvenile myoclonic	24 (11.9)	27 (13.8)	51 (12.8)
Epilepsy with tonic–clonic seizures on awakening	11 (5.5)	12 (6.1)	23 (5.8)
Other idiopathic generalised epilepsy not specified[c]	90 (44.8)	90 (45.9)	180 (45.3)
Other epilepsy syndrome	10 (5.0)	7 (3.6)	17 (4.3)
Seizure history, median (IQR)			
Total number of seizures reported	10 (3–99+)	10 (3–99+)	10 (3–99+)
Days since first seizure	203 (98–665)	250 (110–603)	228 (100–648)
Days since most recent seizure	4 (0–26)	4 (0–25)	4 (0–26)
EEG, *n* (%)			
EEG not done	20 (7.7)	24 (9.2)	44 (8.5)
EEG normal	58 (22.3)	51 (19.6)	109 (21.0)
Non-specific abnormality	11 (4.2)	9 (3.5)	20 (3.8)
Generalised abnormality: slow wave activity with spiking	138 (53.1)	133 (51.2)	271 (52.1)
Generalised abnormality: slow wave activity without spiking	8 (3.1)	7 (2.7)	15 (2.9)
Focal abnormality: paroxysmal slow activity with spiking	10 (3.8)	8 (3.1)	18 (3.5)
Focal abnormality: paroxysmal slow activity without spiking	2 (0.8)	7 (2.7)	9 (1.7)
Other	13 (5.0)	21 (8.1)	34 (6.5)

a Post-traumatic amnesia for > 24 hours or compound depressed fracture.
b More than one category could be selected.
c In this group, 149 of 179 patients (83%) reported tonic–clonic seizures.

The completeness of follow-up statistic (see *Appendix 3*, *Table 38* and *Figure 26*) for the primary outcome was 87% for valproate and 83% for levetiracetam. In this analysis, the median number of days of follow-up was 427 (IQR 365–731) days for the valproate group and 550 (IQR 366–781) days for the levetiracetam group; follow-up was shorter in the valproate group, as participants allocated valproate achieved the primary outcome sooner.

Time to 12-month remission

For the ITT analysis of time to 12-month remission, there is insufficient evidence to conclude non-inferiority of levetiracetam compared with valproate, as the 95% CI for the HR (unadjusted: 1.19, 95% CI 0.96 to 1.47; adjusted: 1.23, 95% CI 0.99 to 1.52) includes the predefined non-inferiority margin of 1.314. There is crossing of the Kaplan–Meier survival curves (*Figure 12*) and evidence of non-equality of HRs across time ($p = 0.001$), violating the assumption of proportional hazards. To supplement presentation of the average treatment effect over time, we also present interval-specific HR estimates (*Table 18*), which indicate a significant beneficial effect of initiating treatment with valproate within the first year. Thereafter there are no statistically significant effects but the direction of benefit is in favour

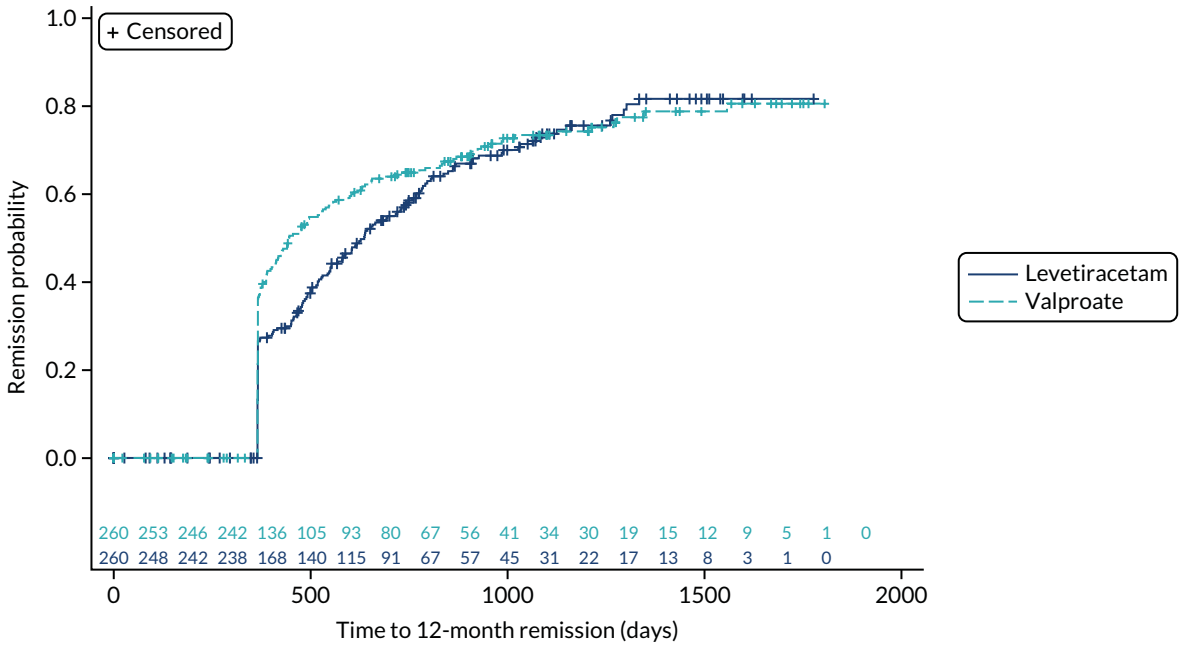

FIGURE 12 Kaplan–Meier plot of time to 12-month remission ITT analysis: levetiracetam vs. valproate for generalised or unclassified epilepsy.

TABLE 18 Hazard ratio estimates for time to 12-month remission

Model and analysis set	Time interval	HR (95% CI)	*p*-value for equality of HR over time
Primary analysis: Cox model with treatment (ITT)	All follow-up[a]	1.19 (0.96 to 1.47)	< 0.01
Cox model with treatment (ITT), gender, number of seizures and centre as random effects	All follow-up[a]	1.23 (0.99 to 1.52)	< 0.01
Cox model with interaction between treatment and categorical time intervals (ITT)	≤ 1	1.68 (1.07 to 2.62)	0.03
	(1–2)	1.26 (0.95 to 1.66)	
	(2–3)	0.57 (0.31 to 1.06)	
	> 3 years[a]	0.70 (0.23 to 2.09)	
Cox model with epilepsy type (generalised/unclassified)	All follow-up[a]	1.19 (0.96 to 1.47)	< 0.01
Fine and Gray model[44] with treatment (PP)	All follow-up[a]	1.68[b] (1.30 to 2.15)	0.51

HR > 1 indicates benefit to valproate.
a Last event time is 1557 days. Last censored time is 1805 days.
b Ratio of rate of occurrence of 12-month remission in patients who are currently event free or who have previously failed randomised treatment.

of valproate during the interval from 1 to 2 years and in favour of levetiracetam during the interval from 2 to 3 years. These results should be viewed cautiously, as they are sensitive to interval choice and subject to selection bias. We also present the annual difference in 12-month remission probabilities (*Table 19*) showing, for example, that at 1 year the proportion of patients entering 12-month remission was 9% lower in the levetiracetam group than in the valproate group. The Kaplan–Meier estimate of the median number of days to achieve 12-month remission was also shorter for valproate (445 days, 95% CI 406 to 531 days) than for levetiracetam (636 days, 95% CI 553 to 728 days).

TABLE 19 Annual outcome probability estimates of seizure outcomes from the ITT analysis: levetiracetam vs. valproate for generalised or unclassified epilepsy

Outcome variable	Events/total	Year 1	Year 2	Year 3	Year 4
12-month remission, number at risk					
Valproate	175/260	240	76	35	13
Levetiracetam	164/260	234	86	31	11
Percentage 12-month remission (95% CI)					
Valproate		36 (30 to 42)	64 (58 to 71)	73 (67 to 79)	79 (72 to 85)
Levetiracetam		26 (21 to 32)	57 (50 to 64)	74 (67 to 80)	82 (75 to 88)
Difference in percentage of 12-month remission: levetiracetam compared with valproate (95% CI)		−9 (−18 to −1)	−7 (−16 to 2)	0 (−8 to 9)	3 (−6 to 12)
Time to 24-month remission, number at risk					
Valproate	103/260	240	213	55	19
Levetiracetam	76/260	234	192	61	17
Percentage 24-month remission (95% CI)					
Valproate			30 (24 to 36)	49 (42 to 56)	55 (47 to 63)
Levetiracetam			18 (13 to 24)	40 (32 to 47)	51 (41 to 60)
Difference in percentage of 24-month remission: levetiracetam compared with valproate (95% CI)			−12 (−20 to −4)	−10 (−20 to 1)	−4 (−17 to 8)
Time to first seizure, number at risk					
Valproate	188/260	86	64	22	4
Levetiracetam	197/260	62	35	11	3
Percentage seizure free (95% CI)					
Valproate		36 (30 to 42)	31 (25 to 36)	23 (17 to 29)	21 (14 to 27)
Levetiracetam		27 (22 to 33)	21 (16 to 26)	18 (13 to 24)	18 (13 to 24)
Difference in percentage seizure free: levetiracetam compared with valproate (95% CI)		−8 (−17 to 0)	−9 (−17 to −2)	−5 (−13 to 4)	−2 (−11 to 6)

The PP analyses for time to 12-month remission (*Figure 13* and see *Table 18*) excluded, patients with major protocol deviations (1%) and patients later diagnosed as 'not epilepsy' (1%) and accounted for treatment failures prior to achieving 12-month remission (32% valproate, 47% levetiracetam). This analysis indicates superiority of valproate over levetiracetam (HR 1.68, 95% CI 1.30 to 2.15). Furthermore, the assumption of constant HR across time appears reasonable in the PP analysis, suggesting that treatment failures prior to remission largely explain the non-constant effect seen in the ITT analysis.

Additional prespecified sensitivity analyses, the results of which are detailed in *Appendix 3*, *Table 39*, did not change the conclusions of the primary analysis.

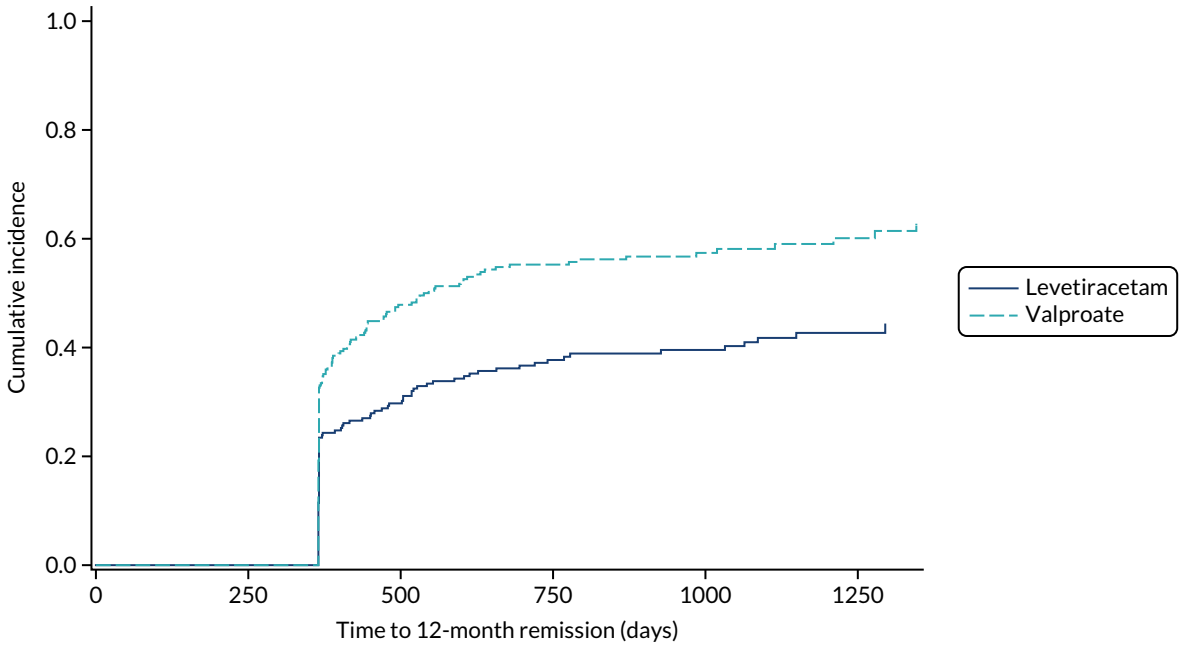

FIGURE 13 Cumulative incidence of time to 12-month remission from competing risks PP analysis: levetiracetam vs. valproate for generalised or unclassified epilepsy.

Subgroup effects were explored in a post hoc analysis (*Figure 14*) and indicate an important advantage for initiating valproate in those with other idiopathic generalised epilepsies (HR 1.55, 95% CI 1.14 to 2.11), as the difference in immediate 12-month remission rates was 19.1% (95% CI 6.6% to 31.7%), but not for absence epilepsies (HR 0.90, 95% CI 0.60 to 1.35) or unclassified epilepsy (HR 1.07, 95% CI 0.69 to 1.67).

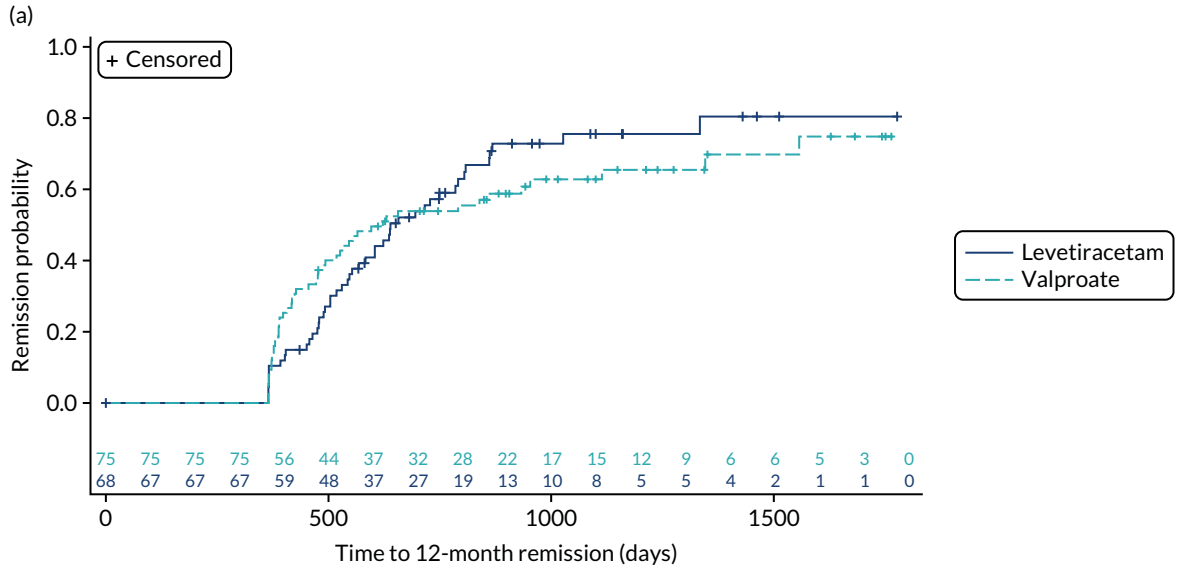

FIGURE 14 Kaplan–Meier plots of time to 12-month remission epilepsy type subgroup analysis: levetiracetam vs. valproate. (a) Absence epilepsy; (b) other generalised epilepsy; and (c) unclassified epilepsy. (*continued*)

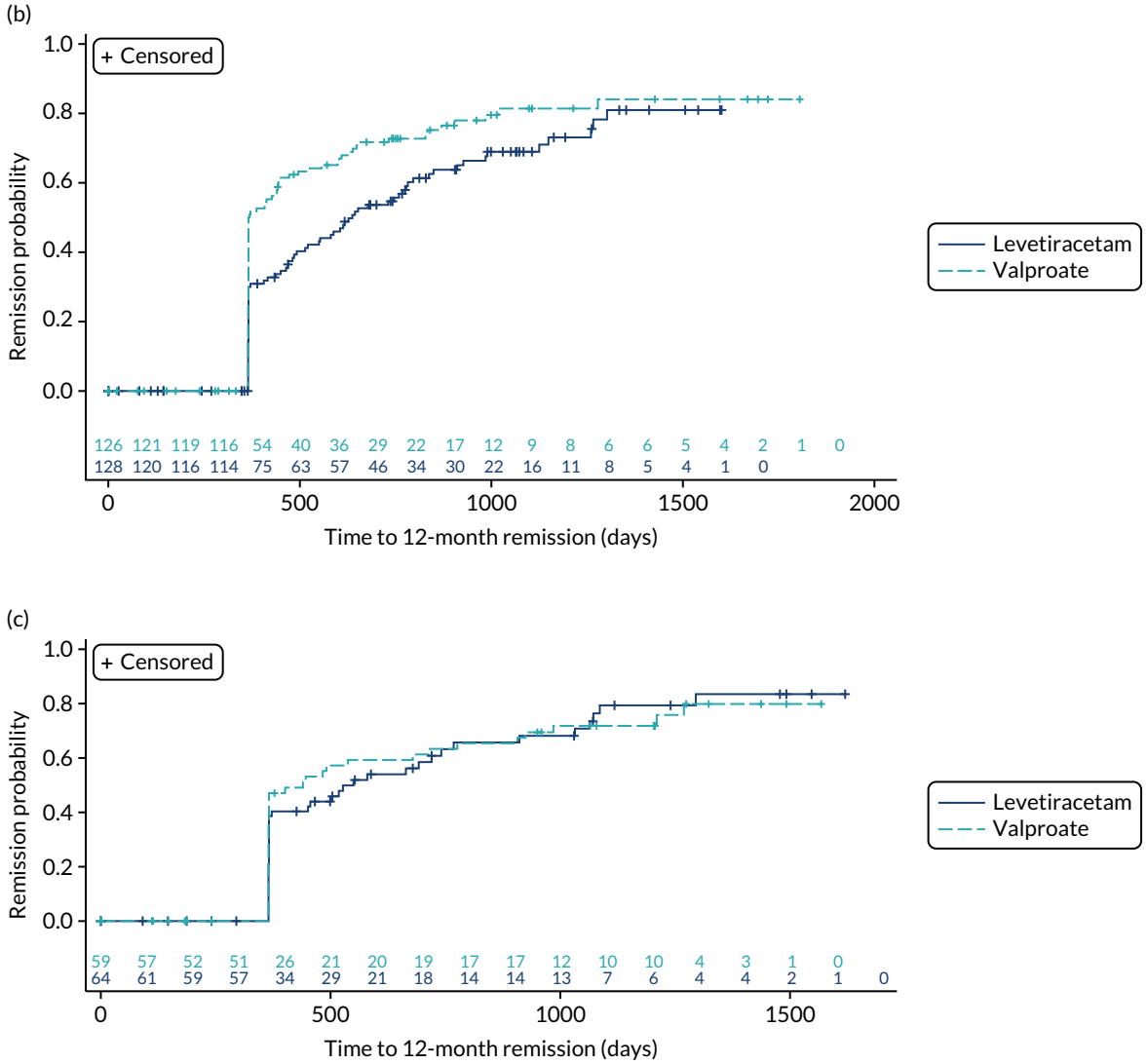

FIGURE 14 Kaplan–Meier plots of time to 12-month remission epilepsy type subgroup analysis: levetiracetam vs. valproate. (a) Absence epilepsy; (b) other generalised epilepsy; and (c) unclassified epilepsy.

Time to 24-month remission

In the ITT analysis of time to 24-month remission, initiating treatment with valproate was superior to initiating treatment with levetiracetam (HR 1.43, 95% CI 1.06 to 1.92). As with time to 12-month remission, there is crossing of the Kaplan–Meier survival curves (*Figure 15*) and evidence of non-equality of HRs across time ($p = 0.002$), suggesting a violation of the assumption of proportional hazards. The difference in 24-month remission rates was −12% (95% CI −20% to −4%) at 24 months' follow-up, diminishing to −4% (95% CI −17% to 8%) at 4 years.

Time to first seizure

For time to first seizure (*Figure 16*), valproate was superior to levetiracetam (HR 0.82, 95% CI 0.67 to 1.00), and there was insufficient evidence to suggest a violation of the assumption of proportional hazards ($p = 0.39$) – most likely because this analysis would not be affected by treatment failures for inadequate seizure control.

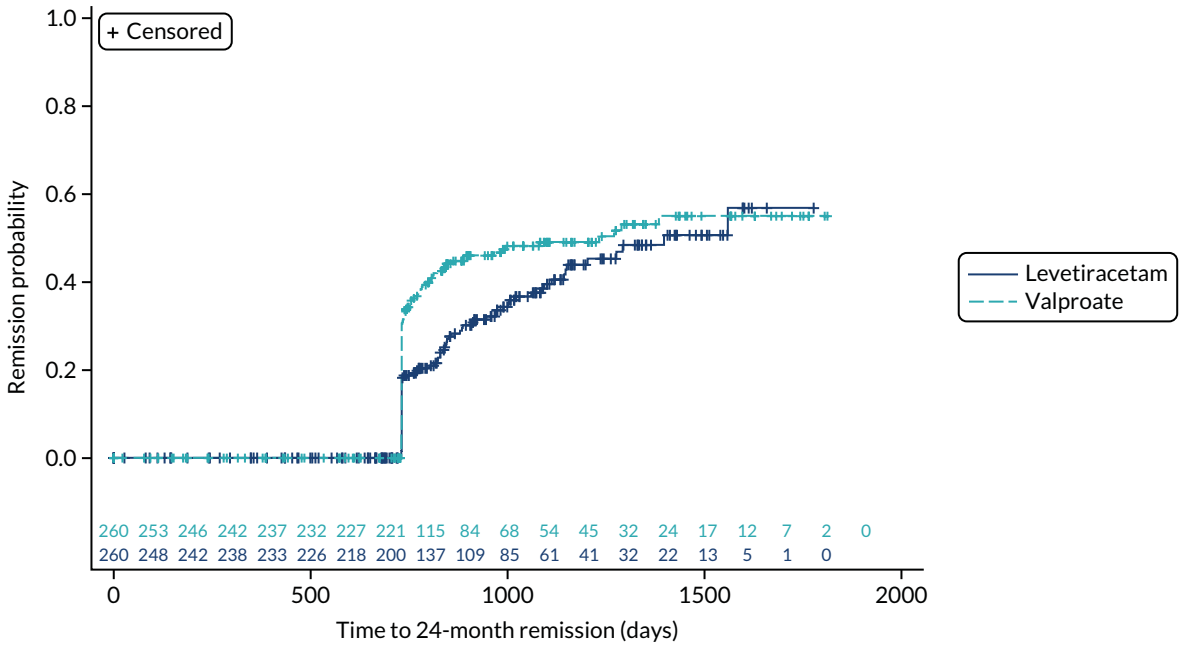

FIGURE 15 Kaplan–Meier plot of time to 24-month remission: levetiracetam vs. valproate for generalised or unclassified epilepsy.

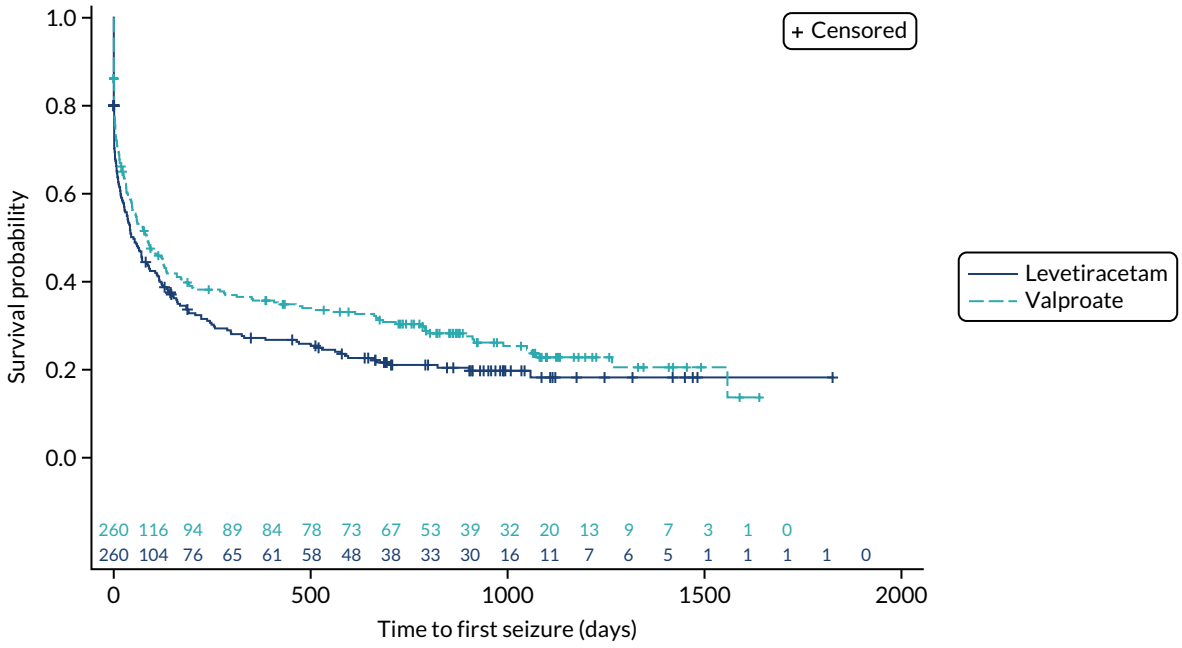

FIGURE 16 Kaplan–Meier plot of time to first seizure: levetiracetam vs. valproate for generalised or unclassified epilepsy.

Time to treatment failure

The analysis of overall time to treatment failure for any reason (*Figure 17*) shows a significant benefit for valproate (HR 0.65, 95% CI 0.50 to 0.83), with no evidence to suggest a violation of the assumption of proportional hazards ($p = 0.22$). *Table 20* provides annual treatment failure rates and differences in failure rates between valproate and levetiracetam. At 2 years there was a difference of −15% (95% CI −23% to −6%) in the treatment failure rate on levetiracetam compared with the treatment failure rate on valproate.

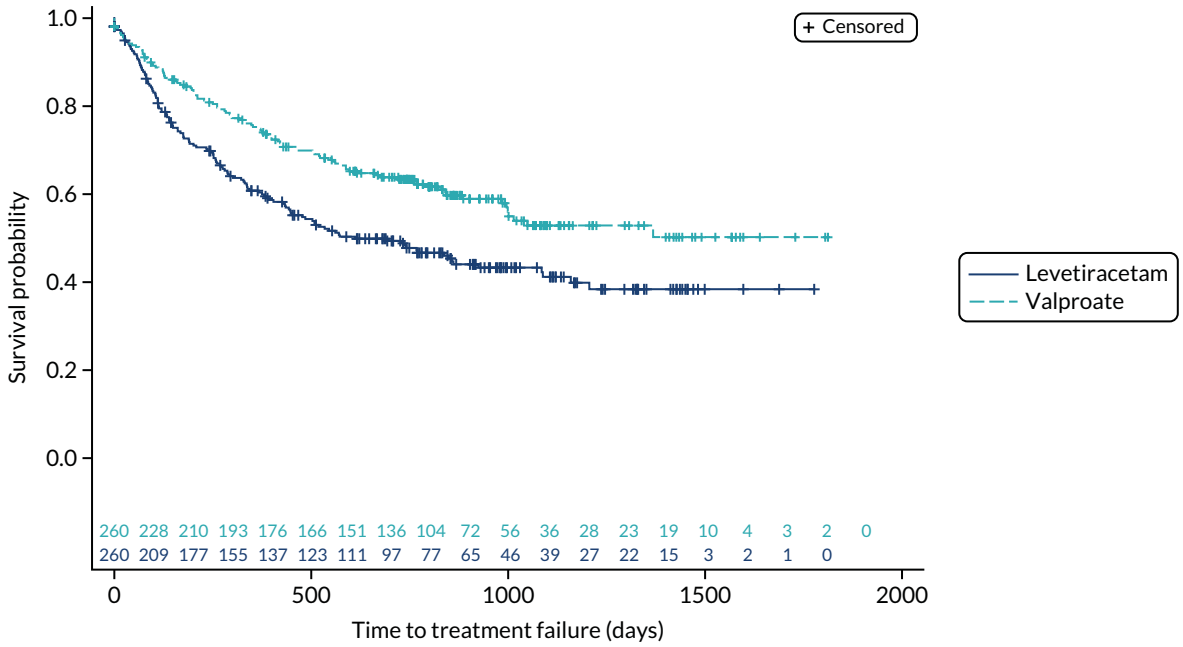

FIGURE 17 Kaplan–Meier plot of time to treatment failure: levetiracetam vs. valproate for generalised or unclassified epilepsy.

TABLE 20 Annual survival probability estimates from ITT analyses of treatment failure: levetiracetam vs. valproate for generalised or unclassified epilepsy

Outcome variable	Events/total	Year 1	Year 2	Year 3	Year 4
Time to treatment failure, number at risk					
Valproate	105/260	185	129	39	13
Levetiracetam	138/260	144	92	39	6
Percentage without failure (95% CI)					
Valproate		75 (69 to 80)	63 (57 to 69)	53 (45 to 60)	50 (42 to 59)
Levetiracetam		61 (55 to 67)	49 (42 to 55)	41 (34 to 48)	38 (31 to 46)
Difference in percentage without failure: levetiracetam compared with valproate (95% CI)		−14 (−22 to −6)	−15 (−23 to −6)	−12 (−22 to −2)	−12 (−23 to 0)
Time to treatment failure for UAR (from competing risk cumulative incidence function): percentage without failure (95% CI)					
Valproate		87 (83 to 91)	83 (78 to 87)	81 (76 to 86)	78 (70 to 86)
Levetiracetam		85 (80 to 89)	81 (76 to 86)	80 (75 to 85)	80 (75 to 85)
Difference in percentage without failure: levetiracetam compared with valproate (95% CI)		−3 (−9 to 4)	−2 (−9 to 5)	−1 (−8 to 6)	2 (−7 to 11)
Time to treatment failure for ISC (from competing risk cumulative incidence function): percentage without failure (95% CI)					
Valproate		91 (87 to 94)	86 (81 to 90)	80 (74 to 86)	80 (74 to 86)
Levetiracetam		78 (73 to 83)	71 (65 to 77)	64 (57 to 71)	61 (53 to 69)
Difference in percentage without failure: levetiracetam compared with valproate (95% CI)		−13 (−20 to −7)	−15 (−22 to −8)	−16 (−26 to −7)	−19 (−29 to −9)

Table 21 summarises the doses taken at treatment failure or last follow-up and indicate that reasonable dose ranges were tried before deciding failure had occurred. The competing risks analysis shows that this difference is predominantly driven by failures due to ISC with a subdistribution (HR 0.43, 95% CI 0.30 to 0.63) (*Figure 18*), whereas there is little difference between treatments for treatment failure due to unacceptable ARs (HR 0.93, 95% CI 0.61 to 1.40) (*Figure 19*).

The HR for overall treatment failure was not consistent across epilepsy types (*Figure 20*), with a significant benefit for valproate for absence (HR 0.58, 95% CI 0.37 to 0.89) and other generalised types of epilepsy (HR 0.44, 95% CI 0.30 to 0.66) but not for unclassified epilepsy (HR 1.44, 95% CI 0.85 to 2.45; test for interaction $p = 0.002$). The competing risks analysis shows a similar pattern of effects for failure due to ISC [absence epilepsies, HR 0.35 (95% CI 0.19 to 0.63); other generalised eplipsy, HR 0.27 (95% CI 0.14 to 0.49); and unclassified epilepsy, HR 2.15 (95% CI 0.79 to 5.86)]. There was no difference between treatments in failure due to UARs by epilepsy type.

Safety

The SANAD II trial recorded data on ARs, which were AEs judged by the treating clinicians to be possibly, probably or definitely caused by anti-seizure medicines. ARs according to the MedDRA System Organ Classification are shown in *Table 22*, and *Appendix 3*, *Table 40*, shows ARs by MedDRA-preferred term.

TABLE 21 Doses taken by participant aged ≥ 12 years at treatment withdrawal or last follow-up

Reason for withdrawal	Valproate group	Levetiracetam group
Inadequate seizure control	*n* = 9	*n* = 27
First follow-up/missing[a]	0	First follow-up = 1
Mean (SD) (mg)	1100 (397)	2304 (866)
Range (mg)	400–1700	1000–4000
Unacceptable AEs	*n* = 28	*n* = 28
First follow-up/missing	First follow-up = 6	First follow-up = 4
Mean (SD) (mg)	1227 (458)	1417 (786)
Range (mg)	600–2000	250–3000
Other reason for withdrawal	*n* = 16	*n* = 9
First follow-up/missing	First follow-up = 5	First follow-up = 6
Mean (SD) (mg)	1036 (518)	1500 (1323)
Range (mg)	500–2400	500–3000
Remission of seizures	*n* = 25	*n* = 15
First follow-up/missing	First follow-up = 1	0
Mean (SD) (mg)	894 (312)	1435 (629)
Range (mg)	200–1500	750–3000
Still on randomised drug	*n* = 100	*n* = 96
First follow-up/missing	Missing = 6	Missing = 6
Mean (SD) (mg)	1129 (424)	1331 (606)
Range (mg)	400–3000	250–3000

a For patients who had withdrawn from a drug at or before first follow-up, no information on the final dose was collected. 'First follow-up' denotes these patients; 'missing' denotes other patients with missing dose information.

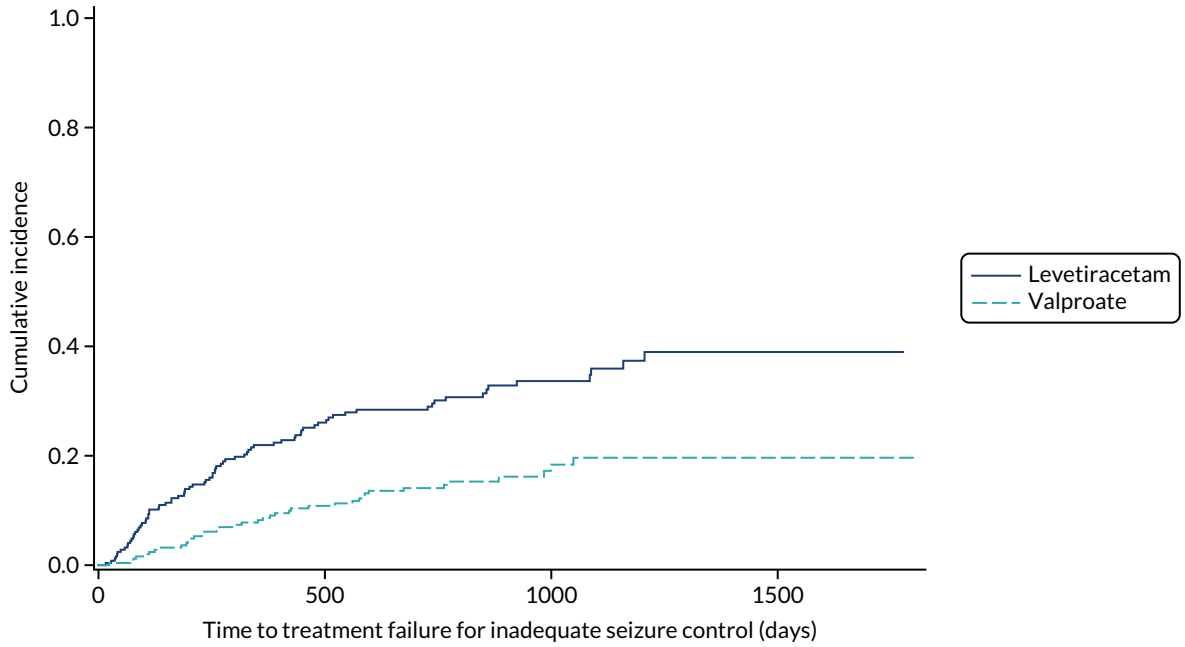

FIGURE 18 Cumulative incidence of treatment failure for ISC from competing risks analysis: levetiracetam vs. valproate for generalised or unclassified epilepsy.

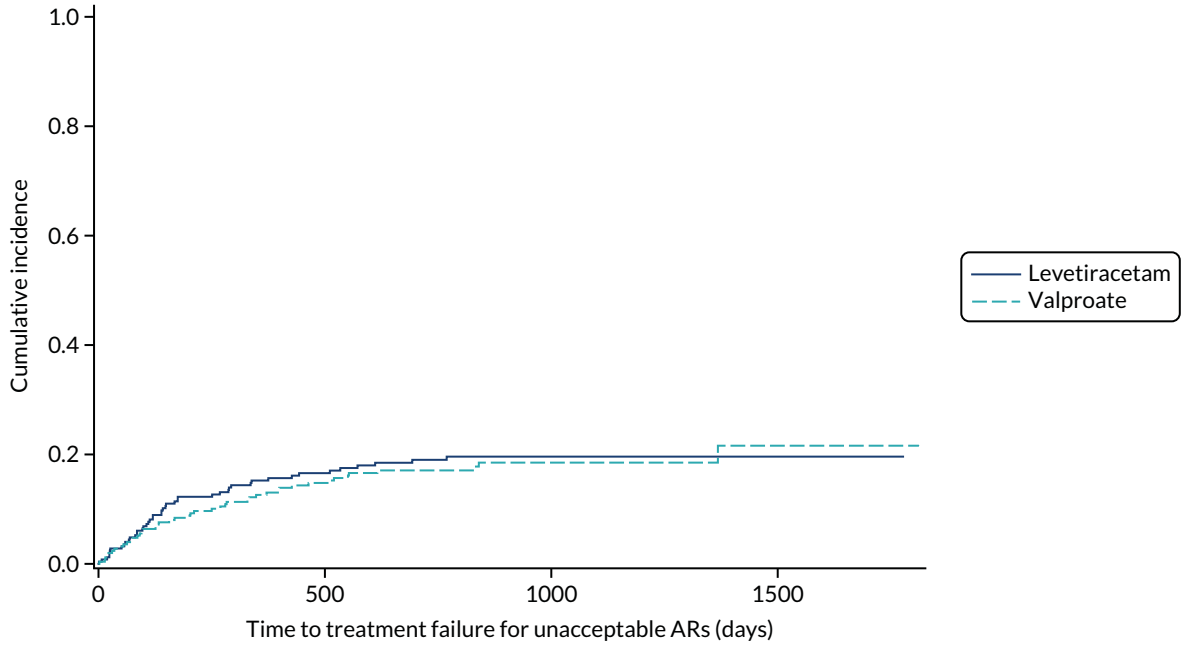

FIGURE 19 Cumulative incidence of treatment failure due to UARs from competing risks analysis: levetiracetam vs. valproate for generalised or unclassified epilepsy.

There were 220 ARs experienced by 96 (37.4%) patients who were randomised to start treatment with valproate and 223 ARs experienced by 107 patients (41.5%) randomised to start treatment with levetiracetam. The profile of ARs is different from most notably psychiatric symptoms reported in those allocated to levetiracetam (109 events, 66 participants) compared with those allocated to valproate (54 events, 36 participants). There were more reports of weight gain in those starting on valproate (26 participants; 10.1%) than in those starting on levetiracetam (eight participants; 3.1%). Of those randomised to start treatment with valproate, 10 (3.9%) had a total of 15 severe ARs and, of those

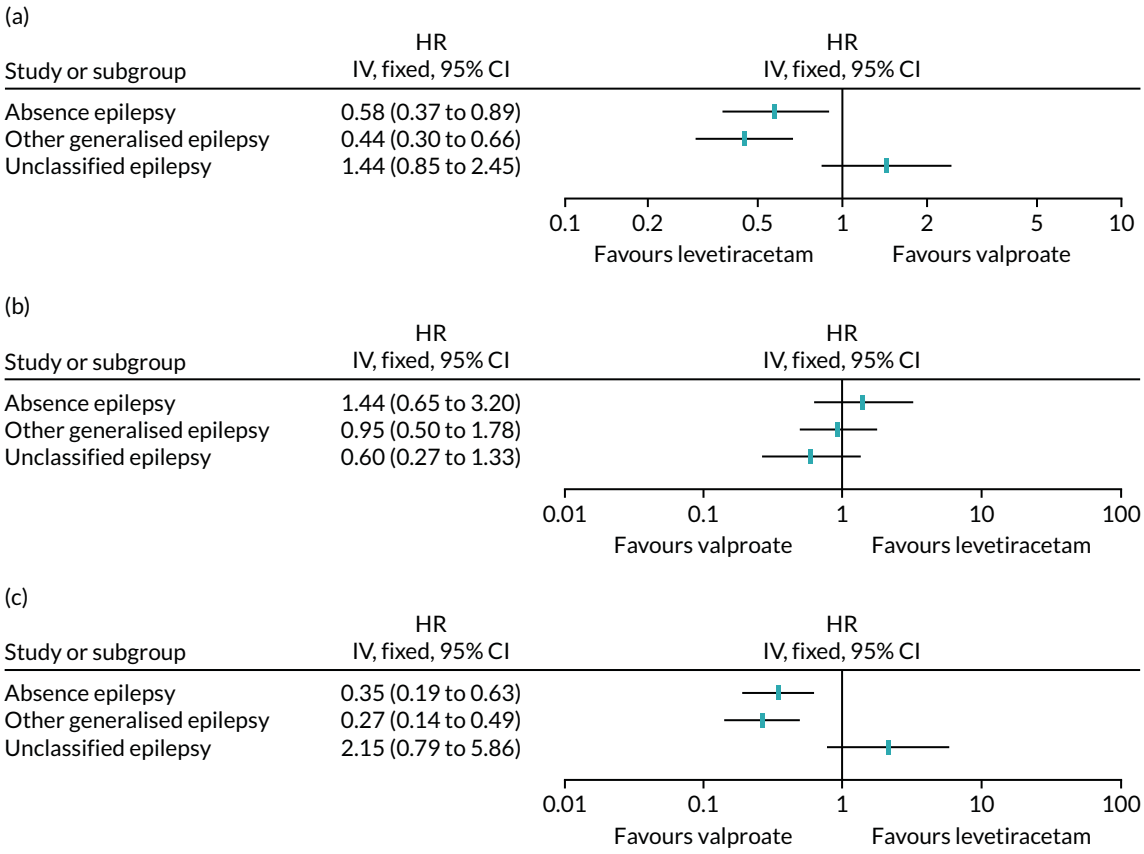

FIGURE 20 Hazard ratios for treatment failure by subgroups: absence epilepsies, other idiopathic generalised epilepsy and unclassified epilepsy. (a) Time to treatment failure any reason; (b) time to treatment failure for UARs; and (c) time to treatment failure for ISC. IV, inverse variance.

randomised to start treatment with levetiracetam, 10 (3.5%) had a total of 16 severe ARs. For two (0.8%) patients on valproate and four (1.6%) patients on levetiracetam, the ARs were classified as serious (see *Appendix 3*, *Table 41*). None of the ARs were classified as SUSARs. There were two deaths, one in each group, that were unrelated to trial treatments (see *Appendix 3*, *Table 42*). One participant randomised to start treatment with valproate became pregnant, and the pregnancy was conceived while taking levetiracetam monotherapy and resulted in a normal healthy baby at postnatal examination. Nine participants randomised to start treatment with levetiracetam reported a pregnancy, which resulted in four normal healthy babies at postnatal examination (levetiracetam, $n = 3$; levetiracetam plus pregabalin being taken at the time of reporting pregnancy, $n = 1$), three miscarriages (all levetiracetam taken at time of reporting pregnancy), one low-birthweight baby (levetiracetam being taken at the time of reporting pregnancy) and one baby with major malformations (carbamazepine being taken at the time of reporting pregnancy) (see *Appendix 3*, *Table 43*).

Quality of life

Of the 520 randomised participants, 299 (58%) returned a baseline QoL questionnaire; the response rate was slightly higher for parents of children aged 5–15 (61% return) than for adults (50% return). At baseline, non-responders were more likely than the responders to be male (71% vs. 57%) and have unclassified epilepsy (27% vs. 19%), and were less likely to have generalised epilepsy (73% vs. 81%). Responders and non-responders were similar in terms of numbers of those with a learning disability or neurological disorder. The response rate diminished substantially after baseline for all subsequent time points, despite sending questionnaires to all participants from the trial office and intervention from the

TABLE 22 Adverse reactions by MedDRA System Organ Classification: levetiracetam vs. valproate for generalised or unclassified epilepsy

MedDRA System Organ Classification	Number of events		Number of patients (%)	
	Valproate group	Levetiracetam group	Valproate group (*N* = 257)	Levetiracetam group (*N* = 258)
Psychiatric disorders	54	109	36 (14.0)	66 (25.6)
Nervous system disorders	58	46	42 (16.3)	37 (14.3)
Gastrointestinal disorders	24	20	19 (7.4)	15 (5.8)
Investigations[a]	31	11	29 (11.3)	11 (4.3)
General disorders and administration site conditions	20	17	16 (6.2)	15 (5.8)
Metabolism and nutrition disorders	19	8	19 (7.4)	8 (3.1)
Skin and subcutaneous tissue disorders	11	6	11 (4.3)	5 (1.9)
Blood and lymphatic system disorders	1	1	1 (0.4)	1 (0.4)
Eye disorders	1	1	1 (0.4)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	0	2	0	2 (0.8)
Congenital, familial and genetic disorders	0	1	0	1 (0.4)
Immune system disorders	1	0	1 (0.4)	0
Injury, poisoning and procedural complications	0	1	0	1 (0.4)

a This category includes weight gain: 27 events in 26 patients (10.1%) on valproate and eight events in eight patients (3.1%) on levetiracetam.

trial management team to reduce the length of the questionnaire and to encourage investigators to provide participants with questionnaires at clinical visits. Results from the repeated measures random-effects models (*Table 23*) suggest that there may be small differences in favour of levetiracetam for the QoL emotional (child), family (child and parent) and school (child) domains. However, because of the high level of missing data, these results cannot be considered as reliable. Imputation was also not considered reasonable because of the high level of missing data.

TABLE 23 Results of longitudinal QoL analyses from mixed models

QoL variable	Number of patients included in analysis,[a] *n* (%)	Treatment effect estimate (valproate vs. levetiracetam) (95% CI)	*p*-value
Adults (potential* N = *208)			
AEs profile	67 (32)	−0.60 (−3.81 to 2.61)	0.714
Anxiety	68 (33)	−1.06 (−2.37 to 0.25)	0.112
Depression	68 (33)	−0.30 (−1.52 to 0.93)	0.633
Mastery	55 (26)	0.34 (−0.91 to 1.59)	0.589
Stigma	56 (27)	0.13 (−1.15 to 1.40)	0.840
Impact	54 (26)	−0.51 (−3.31 to 2.29)	0.718
Overall QoL	55 (26)	−0.61 (−1.28 to 0.06)	0.073

continued

TABLE 23 Results of longitudinal QoL analyses from mixed models (*continued*)

QoL variable	Number of patients included in analysis,[a] *n* (%)	Treatment effect estimate (valproate vs. levetiracetam) (95% CI)	*p*-value
Children (self-reported) (potential* N = *212)			
Attitude to epilepsy	54 (25)	−0.05 (−11.05 to 10.94)	0.992
QoL physical	58 (27)	−2.38 (−12.06 to 7.29)	0.622
QoL emotional	57 (27)	−10.28 (−18.23 to −2.32)	0.012
QoL self-esteem	56 (26)	−6.91 (−16.88 to 3.06)	0.170
QoL social	56 (26)	−6.83 (−16.38 to 2.71)	0.156
QoL family	57 (27)	−9.66 (−17.26 to −2.05)	0.014
QoL school	57 (27)	−11.47 (−20.95 to −1.99)	0.019
Impact of epilepsy	26 (12)	0.01 (−20.74 to 20.77)	0.999
Parent proxy reported (potential* N = *312)			
QoL physical	141 (45)	−2.12 (−7.62 to 3.37)	0.447
QoL emotional	147 (47)	−3.03 (−7.08 to 1.03)	0.143
QoL self-esteem	146 (47)	−4.11 (−8.40 to 0.19)	0.061
QoL social	147 (47)	−1.70 (−5.96 to 2.55)	0.431
QoL family	147 (47)	−3.92 (−7.61 to −0.23)	0.037
QoL school	146 (47)	−3.96 (−8.50 to 0.59)	0.088

a Patients with baseline questionnaire and at least one follow-up questionnaire. Questionnaires returned at time points that did not fall into the prespecified windows are included in this analysis.

Chapter 7 Generalised and unclassified epilepsy results: economic

Data completeness

Hospital Episode Statistics data were available for a total of 412 participants, relating to 202 participants in the valproate treatment group and 210 participants randomised to start treatment with levetiracetam. A breakdown of missing data by treatment group and outcome is provided in *Appendix 4*, *Table 49*.

A total of 389 participants returned at least one self-report questionnaire (completing the resource use, EQ-5D or both sections); 280 participants returned two or more questionnaires. In total, questionnaires were available for 1238 participant-time points (once child and proxy questionnaires had been resolved).

Questionnaires returned after the change in protocol were assigned to their nearest time point for presentation purposes. Self-report resource use data were available for 243 participants at 3 months, 212 at 6 months, 185 at 12 months and 148 at 24 months. Resource use data were also available from 153 questionnaires returned at the later time points (36, 48 and 60 months). It was deemed that there were insufficient data available for any meaningful analysis beyond the primary time horizon of 24 months, and thus the planned 48-month analysis was not conducted.

Utility data (EQ-5D) were available for 274 participants at baseline, and data were interpolated to 12 months for 161 participants and to 24 months for 128 participants. These are lower than the figures reported in *Appendix 4*, *Table 49*, because some 12-month questionnaires were dated before 365 days post randomisation and some 24-month questionnaires were dated before 730 days post randomisation. For the NEWQOL-6D, fewer utility data were available because of a high level of partially completed questionnaires.

A total of 50 data sets were imputed, based on the fraction of missing information 0.7 and accepting $< 1\%$ power fall-off compared with 100 imputations. For the bootstrapped results, this was reduced to 10 for efficiency purposes, accepting a larger reduction in power to achieve an acceptable computation time.[64] Owing to the level of missingness, models containing the NEWQOL-6D were non-convergent; hence only complete-case results are presented for the NEWQOL-6D.

Resource use and costs

Table 24 presents observed mean disaggregated resource use based on the self-report questionnaires. *Table 25* presents the most common outpatient and A&E-related HRGs and costs observed during the trial period. During the 24-month follow-up period, 108 unique HRGs were recorded in admitted patient care, 168 in outpatients and 30 in A&E. The most common inpatient attendances were WJ11Z (disorders of immunity) ($n \approx 35$), PR02C [paediatric epilepsy with a complication or comorbidity (CC) score of 0] ($n \approx 15$) and PR02B (paediatric epilepsy with a CC score of 1–5) ($n \approx 15$).

TABLE 24 Observed resource use based on self-report questionnaire (24-month time horizon)

Resource	Mean [range] (number of participants)							
	3-month time point		6-month time point		12-month time point		24-month time point	
	Valproate group	Levetiracetam group	Valproate group	Levetiracetam group	Valproate group	Levetiracetam group	Valproate group	Levetiracetam group
Questionnaires returned (*n*)	128	115	118	94	99	86	73	75
Primary care								
GP consultation at GP surgery	0.71 [0–10] (47)	0.55 [0–6] (33)	0.61 [0–10] (41)	0.51 [0–6] (27)	0.46 [0–4] (28)	0.65 [0–10] (23)	0.71 [0–20] (23)	0.68 [0–9] (20)
Nurse consultation at GP surgery	0.24 [0–8] (16)	0.30 [0–6] (18)	0.31 [0–10] (21)	0.20 [0–2] (13)	0.35 [0–4] (24)	0.34 [0–10] (12)	0.41 [0–16] (12)	0.64 [0–14] (17)
GP home visit	0.04 [0–4] (2)	0.04 [0–3] (3)	0.01 [0–1] (1)	0	0.03 [0–1] (3)	0.15 [0–10] (2)	0	0.01 [0–10 (1)
Nurse home visit	0.15 [0–5] (15)	0.18 [0–6] (13)	0.08 [0–4] (7)	0.06 [0–3] (4)	0.06 [0–2] (5)	0.15 [0–10] (3)	0.03 [0–1] (2)	0.09 [0–5] (3)
Blood test	0.30 [0–9] (26)	0.30 [0–3] (27)	0.28 [0–4] (21)	0.23 [0–3] (15)	0.28 [0–4] (16)	0.22 [0–3] (16)	0.18 [0–2] (10)	0.15 [0–2] (8)
Urine test	0.10 [0–3] (10)	0.17 [0–3] (13)	0.14 [0–4] (11)	0.13 [0–3] (8)	0.17 [0–2] (14)	0.20 [0–10] (6)	0.07 [0–1] (5)	0.28 [0–12] (8)
Community care								
Health visitor	0.03 [0–2] (3)	0.03 [0–3] (2)	0.02 [0–2] (1)	0.01 [0–1] (1)	0.01 [0–1] (1)	0	0	0.03 [0–2] (1)
Social worker	0.02 [0–2] (2)	0.05 [0–3] (3)	0.03 [0–2] (3)	0.04 [0–4] (1)	0.04 [0–3] (2)	0	0	0.03 [0–1] (2)
Occupational therapist	0.05 [0–3] (5)	0.05 [0–2] (5)	0.05 [0–3] (4)	0.01 [0–1] (1)	0.18 [0–6] (6)	0.03 [0–2] (2)	0.04 [0–1] (3)	0.17 [0–10] (3)
Psychologist	0.02 [0–1] (3)	0.11 [0–7] (4)	0.11 [0–8] (4)	0.10 [0–8] (2)	0.22 [0–12] (5)	0.23 [0–12] (3)	0.10 [0–4] (2)	0.29 [0–10] (4)
Counsellor	0.03 [0–2] (3)	0.24 [0–8] (5)	0.10 [0–3] (6)	0.13 [0–6] (4)	0.12 [0–11] (2)	0.23 [0–6] (6)	0.34 [0–12] (3)	0.28 [0–12] (3)
Physiotherapist	0.08 [0–4] (6)	0.08 [0–3] (4)	0.13 [0–9] (6)	0.06 [0–3] (4)	0.15 [0–5] (4)	0.21 [0–4] (6)	0.11 [0–5] (4)	0.35 [0–20] (3)

Resource	Mean [range] (number of participants)							
	3-month time point		6-month time point		12-month time point		24-month time point	
	Valproate group	Levetiracetam group	Valproate group	Levetiracetam group	Valproate group	Levetiracetam group	Valproate group	Levetiracetam group
Outpatients								
Doctor at hospital	0.84 [0–5] (73)	0.89 [0–6] (61)	0.79 [0–4] (70)	0.73 [0–7] (50)	0.57 [0–3] (40)	0.63 [0–5] (39)	0.58 [0–5] (31)	0.53 [0–5] (30)
Nurse at hospital	0.66 [0–5] (61)	0.65 [0–6] (54)	0.51 [0–3] (49)	0.56 [0–2] (45)	0.44 [0–2] (39)	0.50 [0–4] (31)	0.63 [0–18] (26)	0.37 [0–3] (24)
Ultrasound	0.02 [0–10] (3)	0.04 [0–2] (4)	0.05 [0–2] (4)	0.09 [0–1] (8)	0.03 [0–1] (3)	0.03 [0–2] (2)	0.04 [0–2] (2)	0.07 [0–3] (3)
Radiography	0.07 [0–2] (8)	0.09 [0–3] (8)	0.08 [0–2] (7)	0.07 [0–1] (7)	0.08 [0–3] (6)	0.15 [0–5] (9)	0.05 [0–4] (1)	0.12 [0–4] (5)
CT scan	0.06 [0–1] (8)	0.08 [0–3] (7)	0.03 [0–1] (3)	0.03 [0–1] (3)	0.01 [0–1] (1)	0	0.01 [0–1] (1)	0
MRI scan	0.11 [0–1] (14)	0.23 [0–6] (19)	0.05 [0–2] (5)	0.12 [0–1] (11)	0.01 [0–1] (1)	0	0.01 [0–1] (1)	0.01 [0–1] (1)
EEG	0.23 [0–3] (25)	0.30 [0–6] (26)	0.07 [0–2] (6)	0.07 [0–1] (7)	0.02 [0–1] (2)	0.01 [0–1] (1)	0.03 [0–2] (1)	0
Admitted patient care								
Hospital overnight	0.11 [0–4] (8)	0.10 [0–4] (6)	0.02 [0–1] (2)	0.07 [0–3] (3)	0.05 [0–2] (4)	0.10 [0–6] (4)	0.04 [0–2] (2)	0.07 [0–2] (4)
A&E								
Ambulance	0.23 [0–4] (17)	0.30 [0–5] (23)	0.13 [0–5] (7)	0.21 [0–4] (9)	0.07 [0–1] (7)	0.21 [0–6] (9)	0.15 [0–6] (5)	0.08 [0–2] (4)
A&E visit	0.27 [0–4] (19)	0.45 [0–6] (29)	0.18 [0–3] (15)	0.26 [0–3] (16)	0.18 [0–3] (12)	0.27 [0–8] (13)	0.22 [0–6] (9)	0.33 [0–5] (11)
Other[a]	0.25 [0–] ()	0.34 [0–] ()	0.27 [0–] ()	0.70 [0–] ()	0.14 [0–] ()	0.44 [0–] ()	0.36 [0–] ()	0.28 [0–] ()

ECG, electrocardiography; EEG, electroencephalography; CAMHS, Child and Adolescent Mental Health Services; N/A, not applicable; SENCO, Special Educational Needs Co-ordinator.

a Refers to:

- Primary care: telephone consultation with GP.
- Community care: support worker, family support worker, dentist, hygienist, orthodontist, psychiatrist, dietitian, speech therapist, CAMHS, SENCO, school nurse, hearing test, optician, podiatrist, assistive technology team, sexual health specialist.
- Outpatients: ECG, dual X-ray absorptiometry, sleep apnoea test, peak flow test, venesection.
- Admitted patient care: N/A.
- A&E: walk-in centre.

TABLE 25 Hospital attendances for the most frequent HRG codes (top 10 out of 168) during the 24-month trial period

Service code	Service description	HRG code	Description	Attendances (*n*)[a]		
				Levetiracetam group	Valproate group	Total
Outpatients						
420	Paediatrics	WF01A	Non-admitted face-to-face attendance, follow-up	550	500	1050
400	Neurology	WF01A	Non-admitted face-to-face attendance, follow-up	345	290	640
421	Paediatric neurology	WF01A	Non-admitted face-to-face attendance, follow-up	75	130	205
400	Neurology	WF01B	Non-admitted face-to-face attendance, first	85	70	155
420	Paediatrics	WF01B	Non-admitted face-to-face attendance, first	60	50	110
110	Trauma and orthopaedics	WF01A	Non-admitted face-to-face attendance, follow-up	55	50	110
420	Paediatrics	N/A	N/A	55	30	90
110	Trauma and orthopaedics	N/A	N/A	25	30	55
291	Paediatric neurodisability	N/A	N/A	50	0	50
421	Paediatric neurology	N/A	N/A	25	25	50
A&E						
T01NA	Type 01 non-admitted	VB09Z	Emergency medicine, category 1 investigation with category 1–2 treatment	100	75	170
N/A	N/A	ASS02	See and treat and convey	95	75	170
T01NA	Type 01 non-admitted	VB08Z	Emergency medicine, category 2 investigation with category 1 treatment	40	45	85
T01NA	Type 01 non-admitted	VB11Z	Emergency medicine, no investigation with no significant treatment	35	20	20
T01NA	Type 01 non-admitted	VB07Z	Emergency medicine, category 2 investigation with category 2 treatment	25	20	45
T01A	Type 01 admitted	VB09Z	Emergency medicine, category 1 investigation with category 1–2 treatment	10	15	25
T03NA	Type 03 non-admitted	VB09Z	Emergency medicine, category 1 investigation with category 1–2 treatment	[b]	[b]	20
T04NA	Type 04 non-admitted	VB09Z	Emergency medicine, category 1 investigation with category 1–2 treatment	[b]	[b]	20
T01A	Type 01 admitted	VB07Z	Emergency medicine, category 2 investigation with category 2 treatment	[b]	[b]	15

TABLE 25 Hospital attendances for the most frequent HRG codes (top 10 out of 168) during the 24-month trial period (*continued*)

Service code	Service description	HRG code	Description	Attendances (*n*)[a]		
				Levetiracetam group	Valproate group	Total
T01A	Type 01 admitted	VB08Z	Emergency medicine, category 2 investigation with category 1 treatment	[b]	[b]	10
T01A	Type 01 admitted	VB04Z	Emergency medicine, category 2 investigation with category 4 treatment	[b]	[b]	10
T03NA	Type 03 non-admitted	VB07Z	Emergency medicine, category 2 investigation with category 2 treatment	[b]	[b]	10

N/A, not applicable.
a Rounded to nearest 5.
b Indicates < 10.

Based on the imputed data, the majority of costs relate to secondary care, in particular outpatient clinic attendance (*Table 26*). Anti-seizure medications also account for a high proportion of the total cost. Participants randomised to start treatment with levetiracetam produced higher costs for community care and secondary care, but lower medication costs than those randomised to start treatment with valproate. Total (unadjusted) costs for participants randomised to start treatment with levetiracetam were £4267 (95% CR £3944 to £5462), compared with valproate £4205 (95% CR £3827 to £4956). The difference of £61 (95% CR –£651 to £1230) was not statistically significant.

Based on imputed data, the mean baseline costs were £1067 (95% CI £934 to £1234) in the levetiracetam group and £1088 (95% CI £978 to £1213) in the valproate group The base-case analysis, which adjusted for baseline costs, yielded a 2-year mean total cost of £4350 (95% CR £4136 to £5623) in the levetiracetam group, compared with £4246 (95% CR £3979 to £5090) in the valproate group. This corresponds to an incremental cost of £104 (95% CR –£587 to £1234).

TABLE 26 Aggregated cost totals as per base case (imputed, discounted)

Type of care	Totals (discounted) (£) at 24 months, mean (95% CR)		Difference (£) (95% CR)
	Valproate group	Levetiracetam group	
Primary and community care	1082 (719 to 1471)	940 (843 to 2114)	142 (–356 to 1077)
Primary care	316 (233 to 383)	255 (262 to 523)	61 (–72 to 236)
Community care	765 (436 to 1158)	684 (531 to 1690)	81 (–387 to 971)
Secondary care	2540 (2193 to 2777)	2447 (2275 to 2892)	92 (–332 to 514)
Admitted patient care	590 (407 to 793)	577 (283 to 308)	13 (–250 to 289)
Outpatient	1613 (1482 to 1733)	1594 (1489 to 1750)	19 (–163 to 199)
A&E	336 (225 to 343)	277 (283 to 418)	60 (–30 to 160)
Medicines	646 (676 to 1001)	818 (547 to 840)	–173 (–366 to 61)
Anti-seizure medication	524 (543 to 841)	692 (416 to 663)	–167 (–347 to 32)
Concomitant medication	121 (94 to 212)	127 (83 to 241)	–5 (–98 to 110)
Total	4267 (3944 to 5462)	4205 (3827 to 4957)	61 (–651 to 1230)

Utilities and quality-adjusted life-years

The distributions of participants' responses to the EQ-5D-3L-Y and the NEWQOL-6D questionnaires by randomised treatment group are presented in *Appendix 4*, *Figures 29* and *30*. Based on imputed data, baseline utilities were 0.831 (95% CR 0.779 to 0.850) in the levetiracetam group and 0.811 (95% CR 0.772 to 0.840) in the valproate group. In the base-case adjusted analysis, levetiracetam was associated with a QALY gain of 1.603 years (95% CR 1.500 to 1.631 years), whereas valproate was associated with a QALY gain of 1.637 years (95% CR 1.565 to 1.673 years) over the 2-year time horizon. This corresponds to an incremental QALY gain of −0.035 years (95% CR −0.137 to 0.032 years).

The QALYs based on the NEWQOL-6D were calculated for complete-case data only, over the 2-year time horizon. Levetiracetam was associated with an adjusted QALYs gain of 1.741 years (95% CR 1.695 to 1.784 years), compared with 1.727 years (95% CR 1.697 to 1.779 years) for valproate. This shows levetiracetam to be associated with an incremental QALY gain of 0.015 years (95% CR −0.051 to 0.056 years).

The distribution of responses to the EQ-VAS is presented in *Table 27*. The adjusted analysis based on the EQ-VAS resulted in a QALY gain of 1.453 years (95% CR 1.358 to 1.495 years) for levetiracetam and of 1.464 years (95% CR 1.369 to 1.502 years) for valproate; the incremental QALY of −0.011 years (95% CR −0.103 to 0.077 years) is consistent with the base-case EQ-5D-3L analysis.

Incremental analysis

Based on the point estimate mean costs and QALYs, levetiracetam was both more costly and less effective than valproate, and, therefore, dominated, meaning that it is not considered to be cost-effective. Levetiracetam is associated with a negative incremental NHB (−0.040, 95% CR −0.175 to 0.037) at a cost-effectiveness threshold of £20,000 per QALY.

Sensitivity analysis

Table 28 presents the results of the sensitivity analyses, which are consistent with the base case for all analyses other than the complete-case analysis and NEWQOL-6D analysis, both of which are limited by missing data.

The cost-effectiveness plane, which depicts the joint uncertainty in costs and QALYs, is presented in *Figure 21*. It shows that 62% of simulations were more costly and less effective, 23% were less costly but less effective, 8% were less costly and more effective, and 7% were more costly and more effective.

The cost-effectiveness acceptability curve (*Figure 22*) indicates that the probability of levetiracetam being cost-effective at a cost-effectiveness threshold of £20,000 per QALY is 0.17.

TABLE 27 Responses to the EQ-VAS thermometer by time point (within 90 days) and intervention group

	Valproate group		Levetiracetam group	
Time point	*n*	Mean (95% CI)	*n*	Mean (95% CI)
Baseline	138	0.7934 (0.7625 to 0.8243)	132	0.7510 (0.7146 to 0.7874)
12 months	87	0.8061 (0.7605 to 0.8516)	69	0.7484 (0.6866 to 0.8102)
24 months	65	0.7929 (0.7326 to 0.8533)	58	0.7893 (0.7327 to 0.8459)

TABLE 28 Results of sensitivity and scenario analyses

Sensitivity analysis	Mean (95% CR) Cost (£)	QALYs	NHB at £20,000 per QALY	NHB at £30,000 per QALY	ICER (£ per QALY)
***Base case* (n = *520*)**					
Valproate	4246 (3979 to 5090)	1.637 (1.565 to 1.673)	1.425 (1.323 to 1.464)	1.496 (1.407 to 1.534)	
Levetiracetam	4350 (4136 to 5623)	1.603 (1.500 to 1.631)	1.385 (1.236 to 1.410)	1.458 (1.328 to 1.481)	
Incremental	104 (−587 to 1234)	−0.035 (−0.137 to 0.032)	−0.040 (−0.175 to 0.037)	−0.038 (−0.158 to 0.034)	Dominated
***0% discount rate (costs and QALYs) (base case 3.5%)* (n = *520*)**					
Valproate	4310 (4037 to 5171)	1.666 (1.592 to 1.702)	1.450 (1.346 to 1.490)	1.522 (1.432 to 1.560)	
Levetiracetam	4421 (4203 to 5721)	1.630 (1.526 to 1.659)	1.409 (1.257 to 1.434)	1.483 (1.350 to 1.507)	
Incremental	111 (−596 to 1264)	−0.035 (−0.140 to 0.033)	−0.041 (−0.180 to 0.037)	−0.039 (−0.162 to 0.034)	Dominated
***6% discount rate (costs and QALYs) (base case 3.5%)* (n = *520*)**					
Valproate	4202 (3939 to 5038)	1.618 (1.547 to 1.654)	1.408 (1.307 to 1.447)	1.478 (1.391 to 1.515)	
Levetiracetam	4302 (4091 to 5556)	1.584 (1.483 to 1.612)	1.369 (1.222 to 1.393)	1.441 (1.313 to 1.464)	
Incremental	99 (−584 to 1210)	−0.034 (−0.135, 0.032)	−0.039 (−0.172 to 0.036)	−0.037 (−0.155 to 0.034)	Dominated
***Unadjusted (no covariates) (base case adjusted)* (n = *520*)**					
Valproate	4205 (3827 to 4956)	1.629 (1.553 to 1.671)	1.419 (1.320 to 1.461)	1.489 (1.399 to 1.530)	
Levetiracetam	4267 (3944 to 5462)	1.610 (1.501 to 1.640)	1.396 (1.247 to 1.426)	1.467 (1.335 to 1.496)	
Incremental	61 (−651 to 1230)	−0.020 (−0.132 to 0.050)	−0.023 (−0.162 to 0.065)	−0.022 (−0.149 to 0.057)	Dominated
Complete data (base case imputed) (cost* n = *58; EQ-5D* n = *109)					
Valproate	5489 (3163 to 8881)	1.666 (1.600 to 1.716)	1.391 (1.200 to 1.523)	1.483 (1.345 to 1.578)	
Levetiracetam	4894 (1727 to 6703)	1.675 (1.640 to 1.750)	1.430 (1.343 to 1.625)	1.512 (1.450 to 1.654)	
Incremental	−595 (−6920 to 3252)	0.009 (−0.039 to 0.116)	0.039 (−0.140 to 0.393)	0.029 (−0.098 to 0.286)	Dominated

continued

TABLE 28 Results of sensitivity and scenario analyses (*continued*)

Sensitivity analysis	Mean (95% CR)				ICER (£ per QALY)
	Cost (£)	QALYs	NHB at £20,000 per QALY	NHB at £30,000 per QALY	
PP cohort (n = 509) (base case all participants, ITT) (n = 520)					
Valproate	4240 (3963 to 5081)	1.640 (1.568 to 1.674)	1.428 (1.324 to 1.465)	1.499 (1.409 to 1.534)	
Levetiracetam	4362 (4137 to 5637)	1.603 (1.502 to 1.632)	1.385 (1.236 to 1.410)	1.458 (1.328 to 1.481)	
Incremental	121 (−587 to 1219)	−0.037 (−0.138 to 0.029)	−0.043 (−0.174 to 0.034)	−0.041 (−0.157 to 0.031)	Dominated
NEWQOL-6D (base case EQ-5D) (costs as base case, NEWQOL-6D based on n = 53 complete cases)					
Valproate	4246 (3979 to 5090)	1.727 (1.697 to 1.779)	1.514 (1.453 to 1.565)	1.585 (1.535 to 1.634)	
Levetiracetam	4350 (4136 to 5623)	1.741 (1.695 to 1.784)	1.524 (1.428 to 1.560)	1.596 (1.520 to 1.633)	
Incremental	104 (−587 to 1234)	0.015 (−0.051 to 0.056)	0.009 (−0.085 to 0.064)	0.011 (−0.069 to 0.060)	£7159
EQ-VAS (base case EQ-5D) (n = 520)					
Valproate	4246 (3979 to 5090)	1.464 (1.369 to 1.502)	1.252 (1.134 to 1.283)	1.323 (1.213 to 1.356)	
Levetiracetam	4350 (4136 to 5623)	1.453 (1.358 to 1.495)	1.235 (1.102 to 1.260)	1.308 (1.190 to 1.335)	
Incremental	104 (−587 to 1234)	−0.011 (−0.103 to 0.077)	−0.016 (−0.135 to 0.077)	−0.015 (−0.121 to 0.076)	Dominated
Treating blank responses in the questionnaire as missing (base case: as zero)					
Valproate	4210 (3938 to 5152)	1.637 (1.565 to 1.673)	1.427 (1.330 to 1.453)	1.497 (1.410 to 1.525)	
Levetiracetam	4517 (4206 to 5791)	1.603 (1.500 to 1.631)	1.377 (1.241 to 1.396)	1.452 (1.329 to 1.473)	
Incremental	307 (−473 to 1424)	−0.035 (−0.137 to 0.032)	−0.050 (−0.171 to 0.018)	−0.045 (−0.158 to 0.019)	Dominated

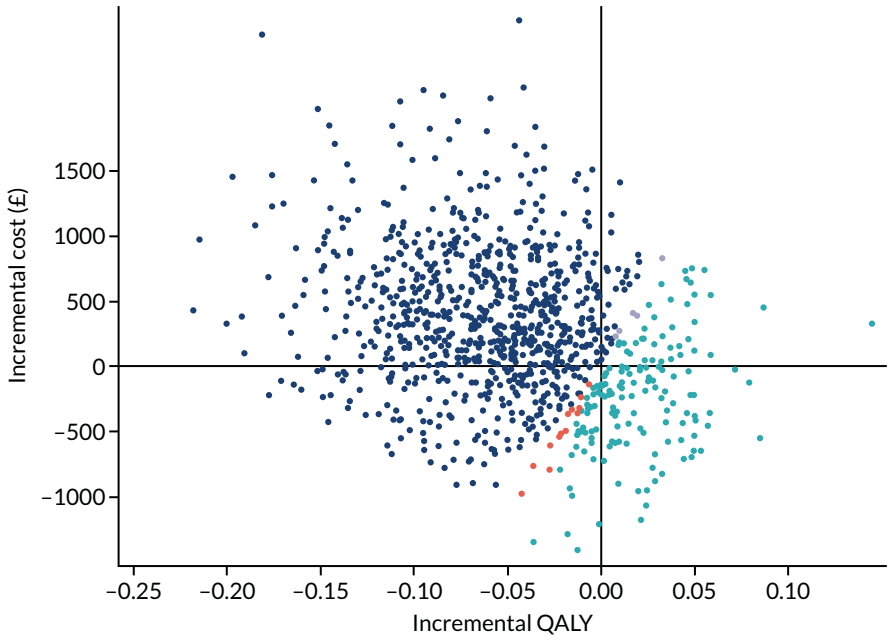

FIGURE 21 Cost-effectiveness plane based on 1000 simulations. Simulations that were cost-effective only at the lower £20,000 per QALY threshold are coloured orange; those which were cost-effective only at the higher £30,000 per QALY threshold are in light purple; those cost-effective at both the £20,000 and £30,000 per QALY thresholds are in light blue; and those that were not cost-effective at either threshold are in dark blue.

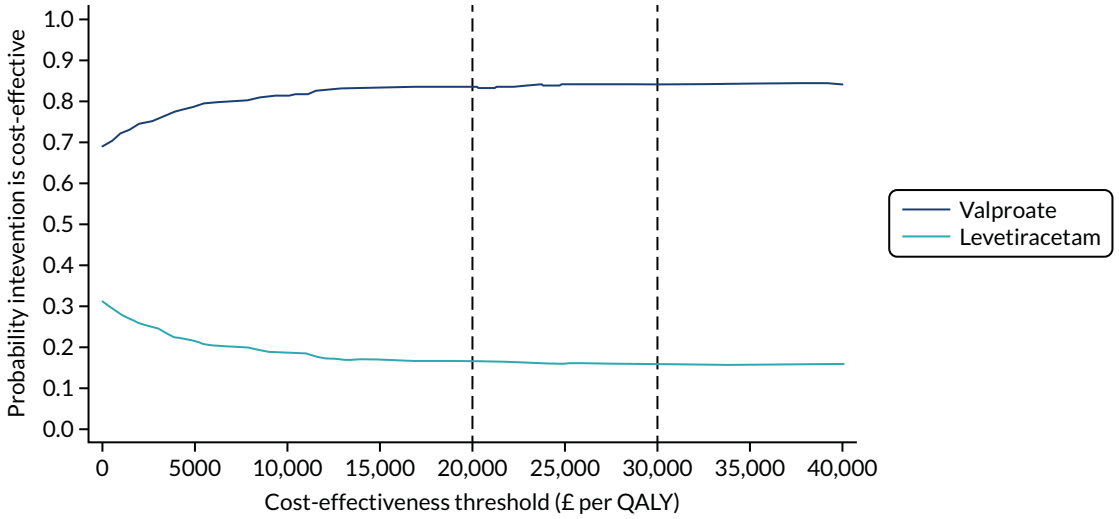

FIGURE 22 Cost-effectiveness acceptability curve.

Subgroup analyses

The results of the subgroup analysis for both children and adults are consistent with the base-case analysis (all participants) and are presented in *Table 29*.

TABLE 29 Results of subgroup analysis

Sensitivity analysis	Mean (95% CR)				
	Total cost (£)	QALYs	NHB at £20,000 per QALY	NHB at £30,000 per QALY	ICER (£ per QALY)
***Base case: all participants* (n = *520*)**					
Valproate	4246 (3979 to 5090)	1.637 (1.565 to 1.673)	1.425 (1.323 to 1.464)	1.496 (1.407 to 1.534)	
Levetiracetam	4350 (4136 to 5623)	1.603 (1.500 to 1.631)	1.385 (1.236 to 1.410)	1.458 (1.328 to 1.481)	
Incremental	104 (−587 to 1234)	−0.035 (−0.103 to 0.077)	−0.040 (−0.175 to 0.037)	−0.038 (−0.158 to 0.034)	Dominated
***Subgroup: children aged < 16 years* (n = *312*)**					
Valproate	4360 (4046 to 5149)	1.626 (1.554 to 1.667)	1.408 (1.307 to 1.455)	1.481 (1.392 to 1.525)	
Levetiracetam	4336 (4017 to 5516)	1.624 (1.506 to 1.646)	1.407 (1.254 to 1.430)	1.479 (1.340 to 1.502)	
Incremental	−24 (−752 to 1065)	−0.002 (−0.123 to 0.054)	−0.001 (−0.151 to 0.069)	−0.002 (−0.136 to 0.062)	Dominated
***Subgroup: adults aged ≥ 16 years* (n = *208*)**					
Valproate	3957 (3525 to 5161)	1.654 (1.563 to 1.693)	1.456 (1.330 to 1.497)	1.522 (1.409 to 1.560)	
Levetiracetam	4316 (3842 to 5898)	1.576 (1.474 to 1.636)	1.360 (1.200 to 1.425)	1.479 (1.291 to 1.492)	
Incremental	359 (−644 to 1640)	−0.078 (−0.175 to 0.015)	−0.096 (−0.232 to 0.025)	−0.090 (−0.208 to 0.018)	Dominated

Chapter 8 Generalised and unclassified epilepsy: discussion

Levetiracetam did not meet our definition of non-inferiority for the primary outcome of time to 12-month remission from seizures for newly diagnosed generalised epilepsy or epilepsy that was unclassified. Levetiracetam was inferior to valproate in terms of time to treatment failure, time to 24-month remission and time to first subsequent seizure. These results are particularly important when considering treatment choices for women of childbearing potential who have newly diagnosed generalised epilepsy, for whom a pregnancy prevention plan has been put in place by the EMA and MHRA[18] because of concerns about teratogenic effects[80–83] and developmental delay/learning difficulties following intrauterine valproate exposure. Levetiracetam has become a common first-choice treatment despite the absence of reliable evidence of its clinical effectiveness compared with valproate.

It is important to highlight that the SANAD II trial was a pragmatic trial that compared the policies of starting treatment with either levetiracetam or valproate, and that drug and dose changes were made during follow-up as per routine clinical practice to maximise seizure control and to minimise ARs. The results for time to 12-month remission indicate an immediate remission rate that is lower with levetiracetam than with valproate (difference of −9%, 95% CI −18% to −1%), but the difference between treatment policies diminishes over time. The higher treatment failure rate associated with levetiracetam is the likely explanation for finding non-proportional hazards. The PP analysis for time to 12-month remission, which took treatment failure into account using a competing risks approach, found superiority of valproate over levetiracetam (HR 1.68, 95% CI 1.30 to 2.15).

For time to treatment failure, valproate was superior to levetiracetam (HR 0.65, 95% CI 0.50 to 0.83). A competing risks analysis shows that the rate of failure due to ARs was similar in the valproate and levetiracetam groups (HR 0.93, 95% CI 0.61 to 1.40), but levetiracetam treatment was significantly more likely to fail because of ISC (HR 0.43, 95% CI 0.30 to 0.63).

To explore the treatment effects further, the cohort was split into three groups: those with absence epilepsies, those with other generalised epilepsies and those with unclassified epilepsy. For time to 12-month remission, survival curves suggest an important disadvantage for starting levetiracetam in the 'other generalised epilepsy' subgroup where the difference in immediate remission rate is −19.1% (95% CI −6.6% to −31.7%). In contrast, there was no clear advantage seen in the absence or unclassified epilepsy subgroups. Those with 'other generalised epilepsies' were mainly those with generalised tonic–clonic seizures, among whom seizure rates are low and in whom many months of observation are typically required to record seizures and make incremental changes to dose and drug. Conversely, absence seizures typically occur at a high rate, enabling more rapid decisions about dose and drug changes in order to gain early seizure control.

For time to treatment failure due to inadequate seizure control, valproate was superior to levetiracetam in patients with absence epilepsies (HR 0.35, 95% CI 0.19 to 0.63) and other generalised epilepsies (HR 0.27, 95% CI 0.14 to 0.49). Conversely, there may be an advantage for starting levetiracetam in those with

unclassified epilepsy (HR 2.15, 95% CI 0.79 to 5.86). The rate of ARs was similar in both treatment arms although the profile was different; the rate of psychiatric coded events was higher in those starting on levetiracetam and weight increase was more common in those starting on valproate.

The SANAD II trial did not exclude the recruitment of females of childbearing potential, who could be recruited following appropriate consent and counselling. The number of females between the age of 12 and 50 years recruited ($n = 80$) was lower than the number of males recruited ($n = 218$), and the EMA and MHRA pregnancy prevention scheme was implemented following the commencement of the study and during most of its recruitment and follow-up period. There were 10 pregnancies during the study, none of which was exposed to valproate. Only one pregnancy occurred among those randomised to start treatment with valproate, suggesting an important impact on fertility choices if women are treated with valproate, choices that may persist after valproate is withdrawn.

Analysis of QoL outcomes does not indicate benefit for either drug, but the return rate of questionnaires was disappointingly low.

The economic analysis indicated that levetiracetam was not cost-effective compared with valproate, being both more costly and less effective. The mean total costs were £4350 (95% CR £4136 to £5623), in the levetiracetam group and £4246 (95% CR £3979 to £5090) in the valproate group. Levetiracetam was associated with a smaller mean QALY gain, at 1.603 years (95% CR 1.500 to 1.631 years), than valproate (mean 1.637 years, 95% CR 1.565 to 1.673 years). The resulting negative INHB (–0.040, 95% CR –0.175 to 0.037) responded with a low probability (0.17) of cost-effectiveness at the NICE threshold of £20,000 per QALY. This result was consistent for both the adult and child subgroups, and robust to some of the modelling assumptions tested in sensitivity analysis. Different results were apparent when considering NEWQOL-6D utilities and complete cases, although these analyses were less reliable because of data missingness.

As with the first SANAD trials,[9,16] we have demonstrated that the NHS in the UK can deliver longer-term pragmatic epilepsy trials, collecting data from neurology services and from primary care. Given the duration of the study, the number of follow-up data available was large; the completeness of the follow-up statistic was 87% in the valproate group and 83% in the levetiracetam group. Nonetheless, the SANAD II trial has a number of limitations. First, it was unblinded, as that was the only feasible way to collect longer-term follow-up data when knowledge of first treatment is required to inform future treatment decisions. This may have influenced decisions about dose and treatment changes, biasing results for time to treatment failure and seizure outcomes. Knowledge of treatment allocated may also have influenced reporting of ARs, and this should be taken into consideration when interpreting, for example, the higher rate of psychiatric events in the levetiracetam group. Initial maintenance doses recommended in the protocol reflected clinical practice at the time that the SANAD II trial was undertaken, which included higher relative doses of levetiracetam in children than in adults. It is possible that the initial maintenance doses chosen introduced a systematic bias, but the similar treatment failure rates due to ARs provide some reassurance. It is also important to acknowledge that there is no RCT evidence to inform choice of the initial maintenance dose of levetiracetam, valproate or, indeed, most other anti-seizure medications. Although 76% of participants were classified as having a generalised epilepsy, only 52% had generalised spike and wave changes on EEG, indicating that some of the remaining 24% may have been misclassified. It is not possible to state whether this might have increased or diminished the treatment effects observed, but it is interesting to note that, in the subgroup analysis for 12-month remission, the estimate in unclassified patients favours levetiracetam. In addition, other than for absence epilepsies, the number of participants classified with a specific generalised epilepsy syndrome at the time of randomisation was small, precluding subgroup analyses for syndromes such as juvenile myoclonic epilepsy. More males than females were recruited (64.8% vs. 35.2%), although there is no reason to expect important differences in response by gender.[7] There was also a low return rate for QoL questionnaires, which diminished our ability to identify the QoL consequences of either policy, which also had an impact on our health economic analysis.

The economic analysis was limited by the poor return of self-report questionnaires. However, for costs this was largely mitigated by the acquisition of HES data and the use of follow-up CRFs for the costs of anti-seizure medicines, which were the main cost drivers. Owing to the AUC methodology, QALYs could be calculated provided two or more EQ-5D questionnaires had been returned. However, for the NEWQOL-6D there were insufficient data to complete imputation; hence only complete-case results could be presented. An additional limitation is that there is no tariff currently available for the EQ-5D-3L-Y or proxy version of the EQ-5D-3L and, therefore, the adult tariff was used throughout for estimating utilities from EQ-5D profiles. This represents a weakness in many economic evaluations of interventions in paediatric populations,[75] although a valuation of children's EQ-5D-3L-Y health states should soon be available.[76] Furthermore, given the chronic nature of epilepsy, the 2-year time horizon was somewhat limited, and the planned analysis over a 4-year time horizon could not be conducted because of limitations resulting from missing data.

These results should be put into context with previous studies, although few studies have assessed the longer-term effectiveness of treatments for generalised epilepsies. SANAD I[16] identified valproate as a first-line treatment, as it was superior to lamotrigine for seizure control and superior to topiramate for treatment failure.[12] An individual patient data network meta-analysis,[15] which included data from the SANAD I trial, failed to show superiority for 12-month remission in generalised epilepsy of any drug among valproate, levetiracetam, gabapentin, phenytoin, carbamazepine, oxcarbazepine, topiramate or phenobarbital, but the results were heavily confounded by classification errors; the original trials probably included a significant number of people whose focal epilepsy was misclassified as generalised epilepsy. Valproate was superior to carbamazepine, topiramate and phenobarbital for treatment failure. To our knowledge, the SANAD II trial is the only trial to date that provides much needed head-to-head data on the longer-term effectiveness of valproate compared with levetiracetam.

The recommendations for research are as follows:

1. A network meta-analysis making both direct and indirect comparisons is required of all available anti-seizure monotherapy trials to provide an overview of the entirety of current evidence regarding clinical effectiveness for generalised epilepsy. This work is under way and funded by NIHR to inform the current NICE epilepsy guidelines update.[79]
2. An economic model is required, utilising results of direct and indirect comparisons, to estimate the comparative cost-effectiveness of currently available treatments for generalised epilepsy.
3. An assessment of women's preferences using economic methods such as discrete choice experiments is required, taking into account clinical effectiveness as well as risk in pregnancy.
4. Prognostic modelling of data from the SANAD I and SANAD II trials is required to explore subgroup effects and to better stratify patients for likely outcome at the time of initiating treatment for generalised epilepsy.
5. Methodological work, utilising data from the SANAD I and SANAD II trials, is required to inform the design of future trials assessing the clinical effectiveness and cost-effectiveness of anti-seizure medications in people with newly diagnosed generalised epilepsy. This includes the possibility of designs using data from the SANAD I and SANAD II trials as historical controls.

In conclusion, these results have important implications for clinical practice and research. These results suggest that, for males with generalised onset seizures, first-line treatment should continue to be valproate. The results also suggest that, for women of childbearing potential, levetiracetam is inferior to valproate, as is lamotrigine (the other commonly prescribed alternative). Regulators, guideline developers, clinicians and patient groups could now consider the benefit-to-risk ratio, particularly for those in our subgroup 'other generalised epilepsy'. Some women, particularly those in whom seizures present a particular hazard, may prefer a drug with greater efficacy notwithstanding the risk of teratogenicity. However, women may prefer a first-line drug that that is safer in pregnancy despite lower efficacy, as indicated in a discrete choice experiment that found women would accept a 5% reduction in 12-month remission probability for 1% reduction in fetal abnormality.[84] Therefore, given

that our ITT results show no differences in 12-month remission rates in the longer term, levetiracetam could be a reasonable first-line treatment for women of childbearing potential with newly diagnosed idiopathic generalised epilepsy. For people with unclassified seizures, no significant difference was found but estimates favour levetiracetam. Future studies should not group generalised and unclassified epilepsy together and the international epilepsy community should identify a better strategy for assessing treatment policies in those with unclassified seizures.

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Publications

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Data-sharing statement

All requests for data (pseudoanonymised and fully anonymous) should be sent to the corresponding author. For data which are not fully anonymous, the decision for data sharing also lies with the trial joint data controllers (University of Liverpool, Walton Centre NHS Foundation Trust and Bangor University). Access to available data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Trial sites and principal investigators

Note that some hospitals have at least two principal investigator names because they either had principal investigator change(s) or recruited both adult and paediatric patients. The principal investigator names within one hospital site are listed in reverse chronological order.

*Recruited both adults and children.

- Aberdeen Royal Infirmary, Aberdeen, UK (Karen Lanyon).
- Addenbrooke's Hospital,* Cambridge, UK (Mark Manford, Manali Chitre and Alasdair Parker).
- Alder Hey Children's Hospital, Liverpool, UK (Nina Swiderska and Richard Appleton).
- Arrowe Park Hospital, Upton, UK (James Pauling and Adrian Hughes).
- Birmingham Children's Hospital, Birmingham, UK (Rajat Gupta).
- Heartlands Hospital, Birmingham, UK (Sadia Hanif and Mostafa Awadh).
- Blackpool Victoria Hospital, Blackpool, UK (Sharmini Ragunathan and Nicola Cable).
- Breightmet Health Centre,* Bolton, UK (Paul Cooper and Dan Hindley).
- Burnley General Teaching Hospital, Burnley, UK (Karl Rakshi).
- Central Middlesex Hospital, London, UK (Sophie Molloy).
- Charing Cross Hospital, London, UK (Michael Johnson).
- Chesterfield Royal Hospital, Chesterfield, UK (Kunle Ayonrinde).
- Countess of Chester Hospital,* Chester, UK (Martin Wilson, Satyanarayana Saladi and John Gibb).
- Craigavon Area Hospital, Craigavon, UK (Lesley-Ann Funston, Damhait Cassidy and Jonathan Boyd).
- Derbyshire Children's Hospital, Derby, UK (Mal Ratnayaka and Hani Faza).
- Derriford Hospital, Plymouth, UK (Martin Sadler).
- Diana Princess of Wales Hospital, Grimsby, UK (Hassan Al-Moasseb).
- Frimley Park Hospital, Frimley, UK (Clare Galtrey and Damien Wren).
- Furness General Hospital, Barrow-in-Furness, UK (Anas Olabi).
- Gloucestershire Royal Hospital, Gloucester, UK (Geraint Fuller).
- Good Hope Hospital, Birmingham, UK (Muhammed Khan and Chetana Kallappa).
- Great Western Hospital, Swindon, UK (Ravi Chinthapalli).
- Gwynedd Hospital,* Bangor, UK (Baba Aji, Rhys Davies and Kathryn Foster).
- The James Cook University Hospital, Middlesbrough, UK (Nikolas Hitiris).
- Leeds General Infirmary, Leeds, UK (Melissa Maguire).
- Leicester Royal Infirmary, Leicester, UK (Nahin Hussain).
- Leighton Hospital, Crewe, UK (Simon Dowson and Julie Ellison).
- Lincoln County, Lincoln, UK (Basil Sharrack).
- Luton & Dunstable University Hospital, Luton, UK (Vandna Gandhi).
- Morriston Hospital, Swansea, UK (Rob Powell).
- New Cross Hospital,* Wolverhampton, UK (Phil Tittensor, Beatrice Summers, Sastry Shashikiran and Penelope J Dison).
- Queen Elizabeth Hospital, Birmingham, UK (Shanika Samarasekera and Doug McCorry).
- Ninewells Hospital, Dundee, UK (Kathleen White).
- Northampton General Hospital, Northampton, UK (Kannan Nithi).
- Peterborough City Hospital, Peterborough, UK (Martin Richardson and Richard Brown).
- Poole General Hospital, Poole, UK (Rupert Page).
- Prince Charles Hospital, Merthyr Tydfil, UK (David Deekollu).
- Queen Alexandra Hospital, Portsmouth, UK (Sean Slaght and Stephen Warriner).
- Queen's Hospital Burton, Burton on Trent, UK (Mansoor Ahmed).
- Queen's Hospital, Romford, UK (Abhijit Chaudhuri).
- Queen's Medical Centre, Nottingham, UK (Gabby Chow).

- Raigmore Hospital, Inverness, UK (Javier Artal and Danute Kucinskiene).
- Royal Albert Edward Infirmary, Wigan, UK (Harish Sreenivasa, Singara Velmurugan and Christos S Zipitis).
- Royal Cornwall Hospital, Truro, UK (Brendan McLean).
- Royal Derby Hospital, Derby, UK (Vaithianathar Lal, Angelous Gregoriou and Paul Maddison).
- Royal Glamorgan Hospital, Ynysmaerdy, UK (Trevor Pickersgill).
- Royal Gwent Hospital, Newport, UK (Joseph Anderson and Charlotte Lawthom).
- Royal Hallamshire Hospital, Sheffield, UK (Steve Howell).
- Royal Hampshire County Hospital, Winchester, UK (Gabriel Whitlingum, Wotjek Rakowicz and Lucy Kinton).
- Royal Hospital for Sick Children Edinburgh, Edinburgh, UK (Alisa McLellan and Nitish Vora).
- Royal Hospital for Children, Glasgow, UK (Sameer Zuberi).
- Royal London Hospital, London, UK (Andrew Kelso).
- Royal Manchester Children's Hospital, Manchester, UK (Imelda Hughes and John Martland).
- Royal Preston Hospital,* Preston, UK (Hedley Emsley and Christian de Goede).
- Royal Stoke University Hospital,* Stoke-on-Trent, UK (R P Singh and Carl-Christian Moor).
- Royal Sussex County Hospital, Brighton, UK (Julia Aram).
- Salford Royal Hospital,* Salford, UK (Rajiv Mohanraj and Kumar Sakthivel).
- Scunthorpe General Hospital, Scunthorpe, UK (Suresh Nelapatla).
- Sheffield Children's Hospital, Sheffield, UK (Chris Rittey).
- Southampton General Hospital, Southampton, UK (Ashwin Pinto).
- Southern General Hospital, Glasgow, UK (John Paul Leach).
- St George's Hospital, London, UK (Hannah Cock).
- Stepping Hill Hospital,* Stockport, UK (Anna Richardson, Erika Houston and Christopher Cooper).
- Sunderland Royal Hospital, Sunderland, UK (Geoff Lawson).
- Tameside General Hospital, Ashton-under-Lyne, UK (Albert Massarano).
- The Walton Centre, Liverpool, UK (Tony Marson).
- Torbay Hospital, Torquay, UK (Indranil Dey).
- University Hospital of North Tees, Stockton-on-Tees, UK (Puthuval Sivakumar).
- University Hospital of South Manchester, Manchester, UK (Lap-Kong Yeung).
- University Hospital of Wales, Cardiff, UK (Philip Smith).
- Warrington Hospital, Warrington, UK (Richard Briggs).
- Whiston Hospital, Prescot, UK (Hemalata Bentur).
- Worcestershire Royal Hospital, Worcester, UK (Tom Heafield).
- Worthing Hospital, Worthing, UK (Anna Mathew).
- Wrexham Maelor Hospital,* Wrexham, UK (Dave Smith and Praveen Jauhari).

The following sites opened but did not recruit:

- Forth Valley Royal Hospital, Larbert, UK (Malcolm Macleod).
- Glan Clwyd Hospital, Bodelwyddan, UK (Mark Doran).
- King's College Hospital, London, UK (Robert Elwes).
- The Robert Jones and Agnes Hunt Orthopaedic Hospital, Oswestry, UK (Richa Kulshrestha).
- Royal Devon & Exeter Hospital, Exeter, UK (Richard Tomlinson).
- Royal Liverpool Hospital, Liverpool, UK (Tony Marson).
- Royal Surrey County Hospital, Guildford, UK (Charlie Moss).
- Royal Victoria Hospital, Belfast, UK (John Craig).
- Southport and Formby District General Hospital, Southport, UK (Udo Wieshmann).

Appendix 2 Key protocol amendments

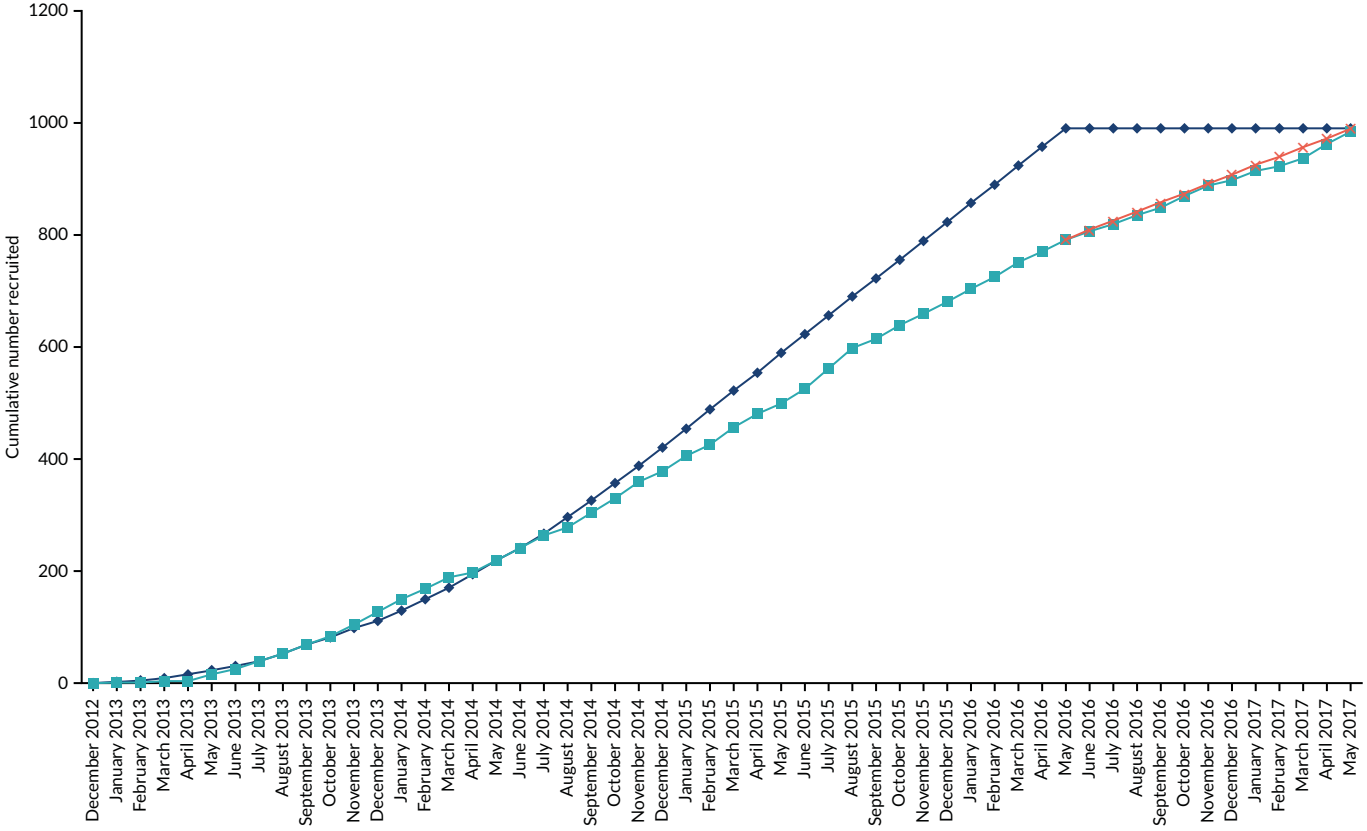
Protocol version and date	Key amendments
1.0 (30 March 2012)	Original approved protocol
2.0 (4 January 2013)	Sections 1 and 5: some of the exclusion criteria were clarified
	Section 2: added new subsection 'Definitions'
	Section 6: screening section amended
	Section 7: dose modifications section amended
	Section 8: QoL and utility assessments section updated
	Section 10: pharmacovigilance section updated to reflect the difference in the reporting procedures for trial and non-trial ASMs
3.0 (7 March 2013)	Contact details for the University of Liverpool updated
	Section 7: text deleted to allow all licensed drug formulations to be used and the initial target maintenance dose for zonisamide amended in *Table 1*
4.0 (13 June 2014)	Sections 1 and 5: two inclusion criteria were amended: • Untreated and not previously treated with anti-seizure medications, except emergency treatment in the past 2 weeks • Willing to provide consent (patient's parent/legal representative willing to give consent where the patient is aged < 16 years or is lacking capacity to consent)
	Sections 5 and 6: text amended to include patients who lack capacity to consent for themselves
	Section 6: the randomisation table was reformatted for clarity and the back-up randomisation system was changed from randomisation envelopes to replica of the randomisation system based on a stand-alone personal computer at CTU
	Section 7: *Table 1* (Arm A. Aged > 12 years) updated by adding 'for 2 weeks' after 50 mg a.m. 100 mg p.m. in the zonisamide column
	Table 2 (Arm A. Children aged 5–12 years) amended for the titration steps and the initial maintenance dose for zonisamide
	Section 8: *Table 6* was updated to include group names in brackets to the age ranges in the column for participant age
	Section 10: the flow chart was updated to reflect the verbatim description by removing unexpected/expected step, as it is done centrally by the chief investigator
	Section 11: updated to include references to the informed consent process in incapacitated adults
5.0 (22 July 2015)	Title page: the NIHR logo updated and a funding statement added
	Protocol approval, contact details and glossary sections were updated
	Section 7: error corrected in the titrating regimen for lamotrigine
	Section 8: to appropriately describe the trial management, the following text: ii) 'collected by Research Nurses from each hospital's patient administration system (PAS)' was replaced with 'accessed as Hospital Episode Statistics (HES) data via the Health and Social Care Information Centre' iii) 'PAS' was replaced with 'HES'
	Section 11: text amended to specify the return time frame for consent forms

Protocol version and date	Key amendments
6.0 (19 May 2017)	Protocol approval and contact details updated
	Section 1: exclusion criteria clarified and study duration updated
	Section 5: new section about withdrawal from the randomised drug added
	Section 6: text about eligibility confirmation was amended for clarity
	Section 10: definition for SUSAR added. Reporting flow chart amended
7.0 (23 August 2017)	Section 8: *Table 5* (trial assessments) updated to allow the follow-up questionnaires issue at site during routine clinic visits
8.0 (28 November 2018)	Signatories and contact details: change to UoL sponsor representative signatory because of retirement of Professor Walley and change to Walton Centre sponsor representative signatory
	Section 4: change to secondary outcomes
	Section 8: QoL and utility assessments updated
	Section 9: updates to text throughout section because of change in secondary outcomes in section 4.2

ASM, anti-seizure medication; CTU, Clinical Trials Unit.

Appendix 3 Further details of results

Additional tables and figures for the focal epilepsy trial



	December 2012	January 2013	February 2013	March 2013	April 2013	May 2013	June 2013	July 2013	August 2013	September 2013	October 2013	November 2013	December 2013	January 2014	February 2014	March 2014	April 2014	May 2014	June 2014	July 2014	August 2014	September 2014	October 2014	November 2014	December 2014	January 2015	February 2015	March 2015	April 2015	May 2015	June 2015	July 2015	August 2015	September 2015	October 2015	November 2015	December 2015	January 2016	February 2016	March 2016	April 2016	May 2016	June 2016	July 2016	August 2016	September 2016	October 2016	November 2016	December 2016	January 2017	February 2017	March 2017	April 2017	May 2017	June 2017
Arm A expected (*n*)	1	2	5	9	14	22	30	39	51	64	77	93	109	128	148	168	191	214	240	266	294	324	355	386	419	452	486	520	553	587	621	654	688	721	755	789	822	856	889	923	957	990	990	990	990	990	990	990	990	990	990	990	990	990	990
Arm A observed (*n*)	0	0	0	0	0	14	22	38	51	67	83	104	126	149	168	187	198	219	240	263	278	304	330	358	377	405	424	456	479	497	524	561	597	615	639	658	679	703	725	750	769	791	805	819	834	849	869	887	898	915	923	937	962	983	990
< 16 years (*n*)	0	0	0	0	0	1	2	4	4	7	9	11	16	20	22	25	28	30	37	38	39	41	42	48	48	55	55	61	65	68	69	77	82	84	85	86	90	96	101	104	106	110	112	117	121	124	131	133	135	136	136	139	143	152	155
Arm A expected (new) (*n*)																																									791	808	824	841	857	874	891	907	924	940	957	973	990	990

FIGURE 23 Recruitment graph for the focal epilepsy trial.

TABLE 30 Completeness of follow-up statistics

Follow-up statistic	Lamotrigine group	Levetiracetam group	Zonisamide group
Completeness of follow-up statistic (%)	77.2	78.3	75.6
Maximum follow-up time (days)			
Median	1482	1492	1488
IQR	1185–1802	1185–1801	1191–1808
Potential follow-up time (days)			
Median	616.5	718	654
IQR	366–1096	366–1096	366–1095
Observed follow-up time (days)			
Median	462.5	449.5	447
IQR	365–777	365–824	365–730
Reverse Kaplan–Meier estimate[a]			
Median	1096	1124	968
IQR	730–1370	730–1461	730–1398
Number (%) withdrawn or lost to follow-up[b]	53 (16.0)	53 (16.0)	59 (18.0)
Number (%) lost to follow-up without treatment failure	38 (11.2)	30 (9.0)	32 (9.8)

a Reverse Kaplan–Meier estimates of follow-up time, with the censoring indicator reversed, so that being censored becomes the outcome of interest.
b Patient is considered lost to follow-up if they have not reached primary outcome, and their final follow-up is > 1 year before the end of the trial. The number includes formal withdrawals who also meet these criteria.

Additional baseline tables and figures for focal epilepsy trial

TABLE 31 Baseline characteristics

Characteristic	Lamotrigine group	Levetiracetam group	Zonisamide group	Total
Age group (deciles) (years), *n* (%)	330	332	328	990
0–9	25 (7.6)	36 (10.8)	28 (8.5)	89 (9.0)
10–19	48 (14.5)	33 (9.9)	40 (12.2)	121 (12.2)
20–29	59 (17.9)	62 (18.7)	48 (14.6)	169 (17.1)
30–39	43 (13.0)	54 (16.3)	59 (18.0)	156 (15.8)
40–49	43 (13.0)	60 (18.1)	56 (17.1)	159 (16.1)
50–59	39 (11.8)	36 (10.8)	28 (8.5)	103 (10.4)
60–69	38 (11.5)	23 (6.9)	33 (10.1)	94 (9.5)
70–79	25 (7.6)	22 (6.6)	20 (6.1)	67 (6.8)
80–89	9 (2.7)	6 (1.8)	16 (4.9)	31 (3.1)
90–99	1 (0.3)	0	0	1 (0.1)

continued

TABLE 31 Baseline characteristics (*continued*)

Characteristic	Lamotrigine group	Levetiracetam group	Zonisamide group	Total
Weight in kg (if aged ≤ 12 years) (*n*)	35	42	41	118
Mean (SD)	32 (10)	30 (8)	32 (14)	31 (11)
Median (IQR)	30 (26–35)	29 (24–35)	28 (23–41)	28 (23–37)
Range	12–55	15–51	15–76	12–76
Missing	5	3	3	11
MRI, *n* (%)				
MRI not done	90 (27.3)	82 (24.7)	86 (26.2)	258 (26.1)
MRI normal	154 (46.7)	176 (53.0)	162 (49.4)	492 (49.7)
Head injury	5 (2.0)	4 (1.5)	3 (1.2)	12 (1.6)
Tumour	4 (1.6)	1 (0.4)	3 (1.2)	8 (1.1)
Cortical dysplasia	1 (0.4)	3 (1.1)	4 (1.6)	8 (1.1)
Hippocampal sclerosis	5 (2.0)	4 (1.5)	3 (1.2)	12 (1.6)
AVM or other vascular malformation (e.g. cavernoma)	7 (2.8)	7 (2.6)	4 (1.6)	18 (2.3)
Infarct	12 (4.7)	11 (4.1)	4 (1.6)	27 (3.5)
Haemorrhage	4 (1.6)	3 (1.1)	2 (0.8)	9 (1.2)
Previous infection (e.g. encephalitis/abscess)	1 (0.4)	2 (0.8)	2 (0.8)	5 (0.7)
Other	53 (17.8)	44 (14.5)	58 (19.0)	155 (17.1)
CT scan, *n* (%)				
CT scan not carried out	213 (64.5)	222 (66.9)	211 (64.3)	646 (65.3)
CT scan normal	80 (24.2)	79 (23.8)	90 (27.4)	249 (25.2)
Head injury	2 (0.7)	1 (0.3)	3 (1.0)	6 (0.7)
Tumour	1 (0.3)	1 (0.3)	2 (0.7)	4 (0.4)
Cortical dysplasia	1 (0.3)	1 (0.3)	0	2 (0.2)
Hippocampal sclerosis	0	1 (0.3)	0	1 (0.1)
AVM or other vascular malformation (e.g. cavernoma)	3 (1.0)	2 (0.7)	1 (0.3)	6 (0.7)
Infarct	5 (1.7)	8 (2.6)	5 (1.6)	18 (2.0)
Haemorrhage	3 (1.0)	3 (1.0)	2 (0.7)	8 (0.9)
Previous infection (e.g. encephalitis/abscess)	3 (1.0)	2 (0.7)	4 (1.3)	9 (1.0)
Porencephalic cyst	1 (0.3)	0	0	1 (0.1)
Other	16 (5.1)	12 (3.8)	11 (3.5)	39 (4.2)

AVM, arteriovenous malformation.

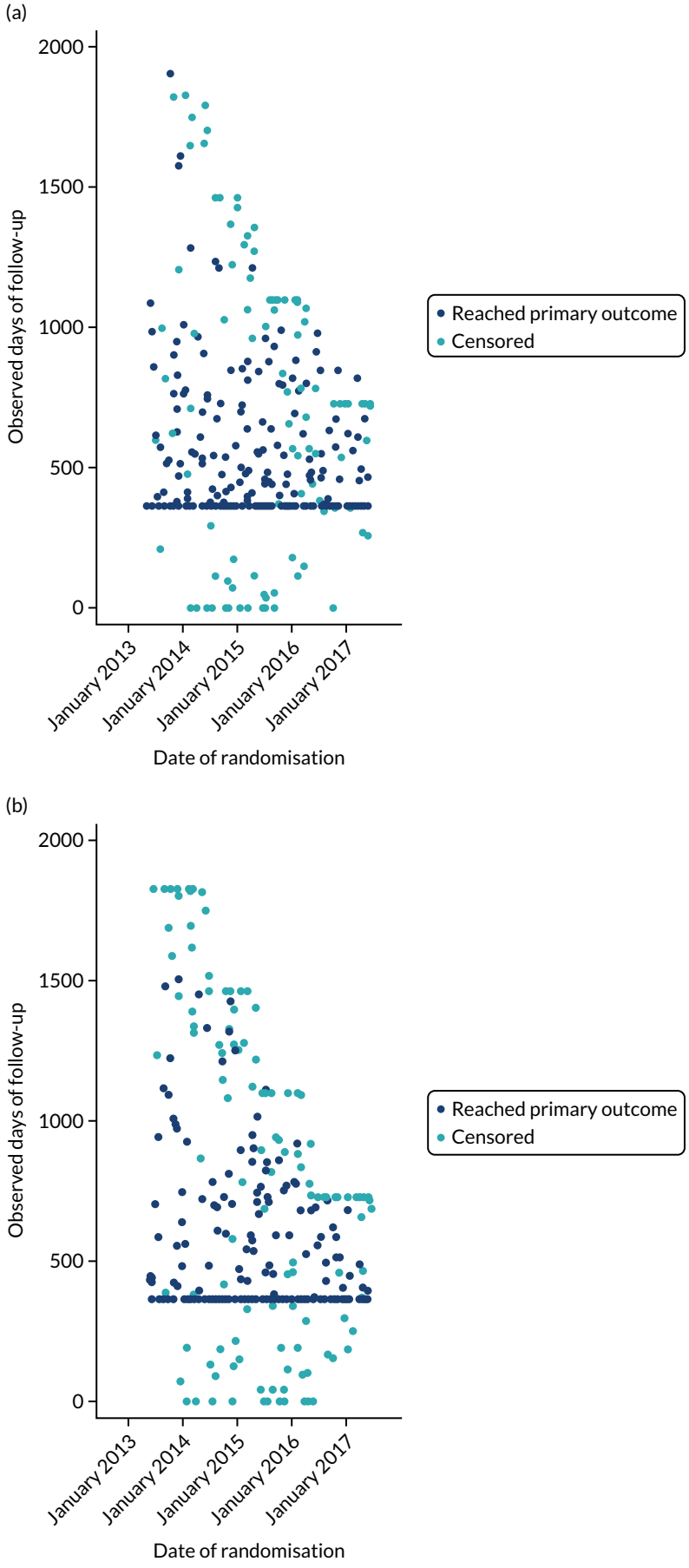


FIGURE 24 Completeness of follow-up scatterplots of observed follow-up time by date of randomisation: focal epilepsy trial. (a) Lamotrigine; (b) levetiracetam; and (c) zonisamide. (*continued*)

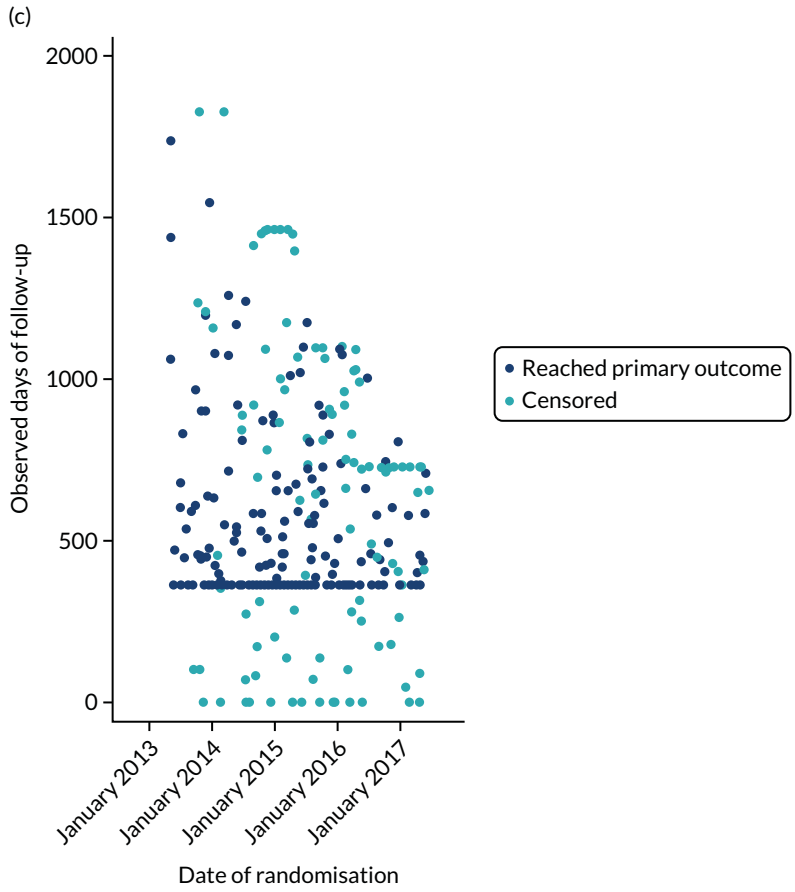


FIGURE 24 Completeness of follow-up scatterplots of observed follow-up time by date of randomisation: focal epilepsy trial. (a) Lamotrigine; (b) levetiracetam; and (c) zonisamide.

TABLE 32 Additional prespecified sensitivity analyses of primary outcome: focal epilepsy

Model and analysis set	Comparison	Time interval	HR (97.5% CI)
Alternative imputation rules	Lamotrigine vs. levetiracetam	All follow-up	1.18 (0.98 to 1.42)
Misdiagnoses excluded (withdrawal reason 'not epilepsy')	Lamotrigine vs. levetiracetam	All follow-up	1.18 (0.95 to 1.47)
Alternative imputation rules	Lamotrigine vs. zonisamide	All follow-up	1.03 (0.86 to 1.23)
Misdiagnoses excluded (withdrawal reason 'not epilepsy')	Lamotrigine vs. zonisamide	All follow-up	1.03 (0.83 to 1.28)

TABLE 33 Adverse reactions by MedDRA-preferred term: focal epilepsy trial

Event MedDRA-preferred term	Number of events			Number of patients (%)		
	Lamotrigine group	Levetiracetam group	Zonisamide group	Lamotrigine group ($n = 328$)	Levetiracetam group ($n = 330$)	Zonisamide group ($n = 324$)
Fatigue	20	31	37	16 (4.9)	29 (8.8)	34 (10.5)
Depressed mood	7	23	17	7 (2.1)	20 (6.1)	16 (4.9)
Irritability	6	29	11	6 (1.8)	29 (8.8)	11 (3.4)
Headache	15	13	17	13 (4.0)	13 (3.9)	16 (4.9)
Memory impairment	10	14	16	9 (2.7)	13 (3.9)	15 (4.6)
Dizziness	13	16	9	13 (4.0)	13 (3.9)	9 (2.8)
Insomnia	14	9	11	12 (3.7)	9 (2.7)	11 (3.4)
Mood altered	6	15	11	6 (1.8)	14 (4.2)	10 (3.1)
Nausea	9	11	10	9 (2.7)	10 (3.0)	10 (3.1)
Rash	17	5	8	16 (4.9)	5 (1.5)	7 (2.2)
Somnolence	11	17	2	10 (3.0)	17 (5.2)	2 (0.6)
Weight decreased	4	5	14	4 (1.2)	5 (1.5)	14 (4.3)
Anxiety	4	9	9	4 (1.2)	9 (2.7)	9 (2.8)
Depression	3	13	5	3 (0.9)	11 (3.3)	5 (1.5)
Aggression	1	12	5	1 (0.3)	12 (3.6)	5 (1.5)
Decreased appetite	2	2	14	2 (0.6)	2 (0.6)	14 (4.3)
Mood swings	2	8	6	2 (0.6)	7 (2.1)	6 (1.9)
Tremor	9	1	5	9 (2.7)	1 (0.3)	5 (1.5)

continued

TABLE 33 Adverse reactions by MedDRA-preferred term: focal epilepsy trial (*continued*)

Event MedDRA-preferred term	Number of events			Number of patients (%)		
	Lamotrigine group	Levetiracetam group	Zonisamide group	Lamotrigine group ($n = 328$)	Levetiracetam group ($n = 330$)	Zonisamide group ($n = 324$)
Vomiting	5	5	4	5 (1.5)	5 (1.5)	4 (1.2)
Anger	2	4	7	2 (0.6)	3 (0.9)	7 (2.2)
Abdominal pain	1	4	6	1 (0.3)	4 (1.2)	6 (1.9)
Disturbance in attention	4	2	5	4 (1.2)	2 (0.6)	3 (0.9)
Pruritus	3	2	6	2 (0.6)	2 (0.6)	6 (1.9)
Sedation	2	2	7	2 (0.6)	2 (0.6)	7 (2.2)
Agitation	1	4	5	1 (0.3)	4 (1.2)	5 (1.5)
Amnesia	3	2	5	3 (0.9)	2 (0.6)	5 (1.5)
Diarrhoea	2	3	5	2 (0.6)	3 (0.9)	5 (1.5)
Weight increased	2	6	2	2 (0.6)	6 (1.8)	2 (0.6)
Dry mouth	6	0	2	6 (1.8)	0	2 (0.6)
Lethargy	3	2	3	3 (0.9)	2 (0.6)	3 (0.9)
Abnormal behaviour	1	4	2	1 (0.3)	4 (1.2)	2 (0.6)
Arthralgia	3	0	4	3 (0.9)	0	4 (1.2)
Balance disorder	2	2	3	2 (0.6)	2 (0.6)	3 (0.9)
Affect lability	1	3	2	1 (0.3)	3 (0.9)	2 (0.6)
Alopecia	1	2	3	1 (0.3)	2 (0.6)	3 (0.9)
Constipation	1	3	2	1 (0.3)	3 (0.9)	1 (0.3)
Dysarthria	3	2	0	2 (0.6)	2 (0.6)	0
Feeling abnormal	1	2	2	1 (0.3)	1 (0.3)	2 (0.6)

Event MedDRA-preferred term	Number of events			Number of patients (%)		
	Lamotrigine group	Levetiracetam group	Zonisamide group	Lamotrigine group ($n = 328$)	Levetiracetam group ($n = 330$)	Zonisamide group ($n = 324$)
Paraesthesia	3	1	1	3 (0.9)	1 (0.3)	1 (0.3)
Abdominal discomfort	0	1	3	0	1 (0.3)	2 (0.6)
Ataxia	3	1	0	3 (0.9)	1 (0.3)	0
Cognitive disorder	1	0	3	1 (0.3)	0	3 (0.9)
Eczema	2	0	2	1 (0.3)	0	1 (0.3)
Palpitations	2	2	0	2 (0.6)	2 (0.6)	0
Poor-quality sleep	0	3	1	0	3 (0.9)	1 (0.3)
Abnormal dreams	3	0	0	3 (0.9)	0	0
Dry skin	0	1	2	0	1 (0.3)	2 (0.6)
Gait disturbance	1	1	1	1 (0.3)	1 (0.3)	1 (0.3)
Hyperhidrosis	0	1	2	0	1 (0.3)	2 (0.6)
Muscle twitching	1	0	2	1 (0.3)	0	1 (0.3)
Nephrolithiasis	0	0	3	0	0	2 (0.6)
Nightmare	3	0	0	3 (0.9)	0	0
Vision blurred	1	0	2	1 (0.3)	0	2 (0.6)
Apathy	1	1	0	1 (0.3)	1 (0.3)	0
Aphasia	0	0	2	0	0	2 (0.6)
Burning sensation	1	0	1	1 (0.3)	0	1 (0.3)
Confusional state	0	1	1	0	1 (0.3)	1 (0.3)
Defiant behaviour	0	2	0	0	2 (0.6)	0

continued

TABLE 33 Adverse reactions by MedDRA-preferred term: focal epilepsy trial (*continued*)

Event MedDRA-preferred term	Number of events			Number of patients (%)		
	Lamotrigine group	Levetiracetam group	Zonisamide group	Lamotrigine group ($n = 328$)	Levetiracetam group ($n = 330$)	Zonisamide group ($n = 324$)
Drug intolerance	0	1	1	0	1 (0.3)	1 (0.3)
Dysgeusia	1	0	1	1 (0.3)	0	1 (0.3)
Dyspepsia	0	1	1	0	1 (0.3)	1 (0.3)
Emotional distress	0	2	0	0	2 (0.6)	0
Gastrointestinal disorder	2	0	0	2 (0.6)	0	0
Hallucination	0	2	0	0	2 (0.6)	0
Hallucination, auditory	0	0	2	0	0	2 (0.6)
Increased appetite	2	0	0	1 (0.3)	0	0
Mouth ulceration	2	0	0	1 (0.3)	0	0
Pain in extremity	1	0	1	1 (0.3)	0	1 (0.3)
Rash generalised	0	2	0	0	2 (0.6)	0
Rash pruritic	1	0	1	1 (0.3)	0	1 (0.3)
Rosacea	2	0	0	1 (0.3)	0	0
Social avoidant behaviour	1	0	1	1 (0.3)	0	1 (0.3)
Suicidal ideation	0	2	0	0	2 (0.6)	0
Thinking abnormal	0	0	2	0	0	2 (0.6)
Visual impairment	0	1	1	0	1 (0.3)	1 (0.3)
Abdominal pain upper	0	0	1	0	0	1 (0.3)
Accidental overdose	1	0	0	1 (0.3)	0	0

Event MedDRA-preferred term	Number of events			Number of patients (%)		
	Lamotrigine group	Levetiracetam group	Zonisamide group	Lamotrigine group ($n = 328$)	Levetiracetam group ($n = 330$)	Zonisamide group ($n = 324$)
Acne	0	0	1	0	0	1 (0.3)
Acute kidney injury	0	0	1	0	0	1 (0.3)
Adverse drug reaction	0	0	1	0	0	1 (0.3)
Bruxism	0	1	0	0	1 (0.3)	0
Contusion	1	0	0	1 (0.3)	0	0
Conversion disorder	0	0	1	0	0	1 (0.3)
Dermatitis allergic	1	0	0	1 (0.3)	0	0
Diplopia	0	0	1	0	0	1 (0.3)
Dissociation	1	0	0	1 (0.3)	0	0
Drooling	0	0	1	0	0	1 (0.3)
Drug eruption	1	0	0	1 (0.3)	0	0
Dry eye	0	0	1	0	0	1 (0.3)
Emotional disorder	0	1	0	0	1 (0.3)	0
Epistaxis	1	0	0	1 (0.3)	0	0
Extrasystoles	0	0	1	0	0	1 (0.3)
Feeling drunk	0	1	0	0	1 (0.3)	0
Frustration tolerance decreased	0	0	1	0	0	1 (0.3)
Gout	0	0	1	0	0	1 (0.3)
Haematemesis	0	1	0	0	1 (0.3)	0
Hair texture abnormal	1	0	0	1 (0.3)	0	0
Head discomfort	0	1	0	0	1 (0.3)	0

continued

TABLE 33 Adverse reactions by MedDRA-preferred term: focal epilepsy trial (*continued*)

Event MedDRA-preferred term	Number of events			Number of patients (%)		
	Lamotrigine group	Levetiracetam group	Zonisamide group	Lamotrigine group ($n = 328$)	Levetiracetam group ($n = 330$)	Zonisamide group ($n = 324$)
Hyperventilation	0	0	1	0	0	1 (0.3)
Hypoaesthesia	0	0	1	0	0	1 (0.3)
Hypohidrosis	0	0	1	0	0	1 (0.3)
Hypothyroidism	0	1	0	0	1 (0.3)	0
Influenza-like illness	0	1	0	0	1 (0.3)	0
Limb discomfort	0	1	0	0	1 (0.3)	0
Lip pain	1	0	0	1 (0.3)	0	0
Loss of libido	0	0	1	0	0	1 (0.3)
Malaise	0	0	1	0	0	1 (0.3)
Migraine	0	0	1	0	0	1 (0.3)
Mouth swelling	0	0	1	0	0	1 (0.3)
Myalgia	0	0	1	0	0	1 (0.3)
Nasal valve collapse	0	1	0	0	1 (0.3)	0
Obsessive–compulsive disorder	0	0	1	0	0	1 (0.3)
Orthostatic hypotension	1	0	0	1 (0.3)	0	0
Panic attack	0	1	0	0	1 (0.3)	0
Parkinson's disease	1	0	0	1 (0.3)	0	0
Parosmia	0	0	1	0	0	1 (0.3)
Peripheral swelling	0	0	1	0	0	1 (0.3)
Personality change	0	0	1	0	0	1 (0.3)

Event MedDRA-preferred term	Number of events			Number of patients (%)		
	Lamotrigine group	Levetiracetam group	Zonisamide group	Lamotrigine group (*n* = 328)	Levetiracetam group (*n* = 330)	Zonisamide group (*n* = 324)
Pollakiuria	1	0	0	1 (0.3)	0	0
Polydipsia	0	0	1	0	0	1 (0.3)
Polyuria	0	0	1	0	0	1 (0.3)
Premature delivery	0	0	1	0	0	1 (0.3)
Presyncope	1	0	0	1 (0.3)	0	0
Psychomotor hyperactivity	0	1	0	0	1 (0.3)	0
Pyrexia	1	0	0	1 (0.3)	0	0
Rash papular	0	0	1	0	0	1 (0.3)
Restless legs syndrome	1	0	0	1 (0.3)	0	0
Seizure	0	1	0	0	1 (0.3)	0
Sleep disorder	1	0	0	1 (0.3)	0	0
Speech disorder	1	0	0	1 (0.3)	0	0
Stevens–Johnson syndrome	0	1	0	0	1 (0.3)	0
Suicide attempt	0	0	1	0	0	1 (0.3)
Swelling face	0	0	1	0	0	1 (0.3)
Swollen tongue	1	0	0	1 (0.3)	0	0
Tearfulness	0	1	0	0	1 (0.3)	0
Tinnitus	0	1	0	0	1 (0.3)	0
Urinary incontinence	0	0	1	0	0	1 (0.3)
Weight gain poor	0	0	1	0	0	1 (0.3)
Wheezing	0	0	1	0	0	1 (0.3)
Total number of events and patients with at least one AR	251	328	351	108 (32.9)	144 (43.6)	146 (45.1)

TABLE 34 Line listings of SARs in focal epilepsy trial

Description	Seriousness	Severity	Suspect anti-seizure medication	Expectedness	Relationship: principal investigator assessment	Relationship: chief investigator assessment	Withdrawn from study drug	Outcome
Randomised to start treatment with lamotrigine								
1: vomiting	Required hospitalisation	Severe	Valproate	Expected	Probably	Possibly	Yes	Resolved
			Lamotrigine	Expected	Unlikely	Possibly	No	
2: ataxia	Required hospitalisation	Moderate	Lamotrigine	Expected	Possibly	Possibly	No	Resolved
Randomised to start treatment with levetiracetam								
3: vomiting	Required hospitalisation	Moderate	Zonisamide	Expected	Possibly	Possibly	Yes	Resolved
Randomised to start treatment with zonisamide								
4: nephrolithiasis	Required hospitalisation	Moderate	Zonisamide	Expected	Probably	Probably	Yes	Resolved
5: suicide attempt	Medically significant/ Important	Moderate	Zonisamide	Expected	Possibly	Possibly	Temporary interruption	Resolved
6: acute kidney injury	Required hospitalisation	Severe	Zonisamide	Expected	Possibly	Possibly	Yes	Resolved
7: premature delivery	Medically significant/ Important	Severe	Zonisamide	Expected	Possibly	Possibly	No	Resolved with sequelae

TABLE 35 Details of deaths in the focal epilepsy trial

Days from randomisation to death	Age at death (years)	Cause of death	Possibly related to trial treatments?
Randomised to start treatment with lamotrigine			
338	51	Cardiac arrest; epileptic seizure	No
7	14	Sudden unexpected death in epilepsy	No
589	47	Status epilepticus; natural causes	No
771	67	Fall down stairs, found at bottom of stairs, blood on face and ear	No
1126	69	Metastatic cancer of kidney	No
39	83	Congestive heart failure	No
697	82	Alzheimer's disease	No
41	88	Severe aortic stenosis	No
1500	64	Cardiorespiratory arrest; end-stage renal failure	No
291	28	Sudden unexpected death in epilepsy; abnormal blood levels of prescribed medications (levetiracetam not detected, elevated sertraline levels)	No
183	53	Large haemorrhagic stroke; hypertension	No
1115	54	Acute myocardial infarction; coronary artery disease; severe fatty liver	No
1779	83	Vascular dementia	No
1355	70	Bronchopneumonia	No
413	72	Progressive metastatic neuroendocrine malignancy	No
Randomised to start treatment with levetiracetam			
461	44	Glioblastoma	No
274	66	Cancer of the pancreas and metastatic spread	No
177	54	Sudden expected death in epilepsy	No
1221	88	Pneumonia	No
254	53	Ischaemic event probably coronary	No
1815	66	Bladder cancer	No
112	51	Glioblastoma multiforme	No
34	39	Hypoxic brain injury; asystolic cardiac arrest (unwitnessed)	No
256	65	Pneumonia; anterior circulation stroke	No
749	24	Intracerebral haemorrhage due to rupture of arteriovenous malformation	No
424	39	Sudden unexplained death in epilepsy	No
311	24	Patient died at home. Referred to the coroner. Had been admitted to hospital on 17 August 2016 via A&E. Breathlessness. Self-discharged before respiratory review. Working diagnosis in A&E was infected, exacerbation of asthma	No

continued

TABLE 35 Details of deaths in the focal epilepsy trial (*continued*)

Days from randomisation to death	Age at death (years)	Cause of death	Possibly related to trial treatments?
Randomised to start treatment with zonisamide			
644	84	Lower respiratory tract infection; immobility; cervical myelopathy	No
264	60	Pulmonary embolism	No
1600	85	Multiorgan failure; hypoperfusion; status epilepticus	No
547	75	Hypertensive heart disease	No
1746	87	Old age; vascular dementia	No
352	83	Colon cancer	No
509	81	Pneumonia; acute renal failure; malignant neoplasm of rectum	No
216	67	Found dead at home	No
341	48	Epilepsy	No
530	66	Chronic obstructive pulmonary disease	No

TABLE 36 Details of pregnancies in the focal epilepsy trial

Patient ID	Day of pregnancy report[a]	Age at date of report (years)	Estimated day of delivery[a]	Day of delivery/ miscarriage[a]	Outcome	Randomised drug	Drug regimen when pregnancy reported
1	113	28	308	344	Normal postnatal examination	Lamotrigine	Lamotrigine
2	239	26	341	302	Normal postnatal examination	Lamotrigine	Lamotrigine
3	1416	36	1604	1580	Normal postnatal examination	Lamotrigine	Lamotrigine
4	826	30	1002	995	Normal postnatal examination	Lamotrigine	Lamotrigine
5	1113	26	1290	1287	Normal postnatal examination	Lamotrigine	Lamotrigine
6	1272	31	1472	1470	Normal postnatal examination	Lamotrigine	Lamotrigine
7	464	30	704	678	Minor malformations	Lamotrigine	Carbamazepine and clobazam
8	1246	20	1484	1476	Normal postnatal examination	Lamotrigine	Levetiracetam

TABLE 36 Details of pregnancies in the focal epilepsy trial (*continued*)

Patient ID	Day of pregnancy report[a]	Age at date of report (years)	Estimated day of delivery[a]	Day of delivery/ miscarriage[a]	Outcome	Randomised drug	Drug regimen when pregnancy reported
9	497	27	650	649	Normal postnatal examination	Lamotrigine	Lamotrigine
10	1351	31	1582	1585	Normal postnatal examination	Lamotrigine	Levetiracetam
11	1245	19	1436	1439	Normal postnatal examination	Lamotrigine	No anti-seizure medication
12	863	35	1046	1051	Normal postnatal examination	Levetiracetam	Lamotrigine
13	351	29	545	534	Normal postnatal examination	Levetiracetam	Levetiracetam
14	2041	30	Missing	2024	Termination	Levetiracetam	Levetiracetam
15	679	33	908	905	Normal postnatal examination	Levetiracetam	Levetiracetam
16	407	38	480	471	Normal postnatal examination	Levetiracetam	Levetiracetam
16	1023	40	1198	1185	Normal postnatal examination	Levetiracetam	Lamotrigine
17	362	38	512	504	Normal postnatal examination	Zonisamide	Levetiracetam
18	30	34	154	38	Planned abortion	Zonisamide	Lamotrigine
19	356	34	640	419	Miscarriage	Zonisamide	Zonisamide
19	811	35	Missing	811	Miscarriage	Zonisamide	Zonisamide
20	1148	27	1298	1301	Normal postnatal examination	Zonisamide	Zonisamide
21	664	39	Missing	706	Miscarriage	Zonisamide	Zonisamide
21	1099	41	1318	1115	Miscarriage	Zonisamide	Lamotrigine
22	170	24	429	180	Miscarriage	Zonisamide	Zonisamide Lamotrigine
23	366	44	Missing	275	Miscarriage	Zonisamide	Zonisamide
23	559	44	798	576	Miscarriage	Zonisamide	Zonisamide
24	1091	25	1302	1306	Normal postnatal examination	Zonisamide	Lamotrigine

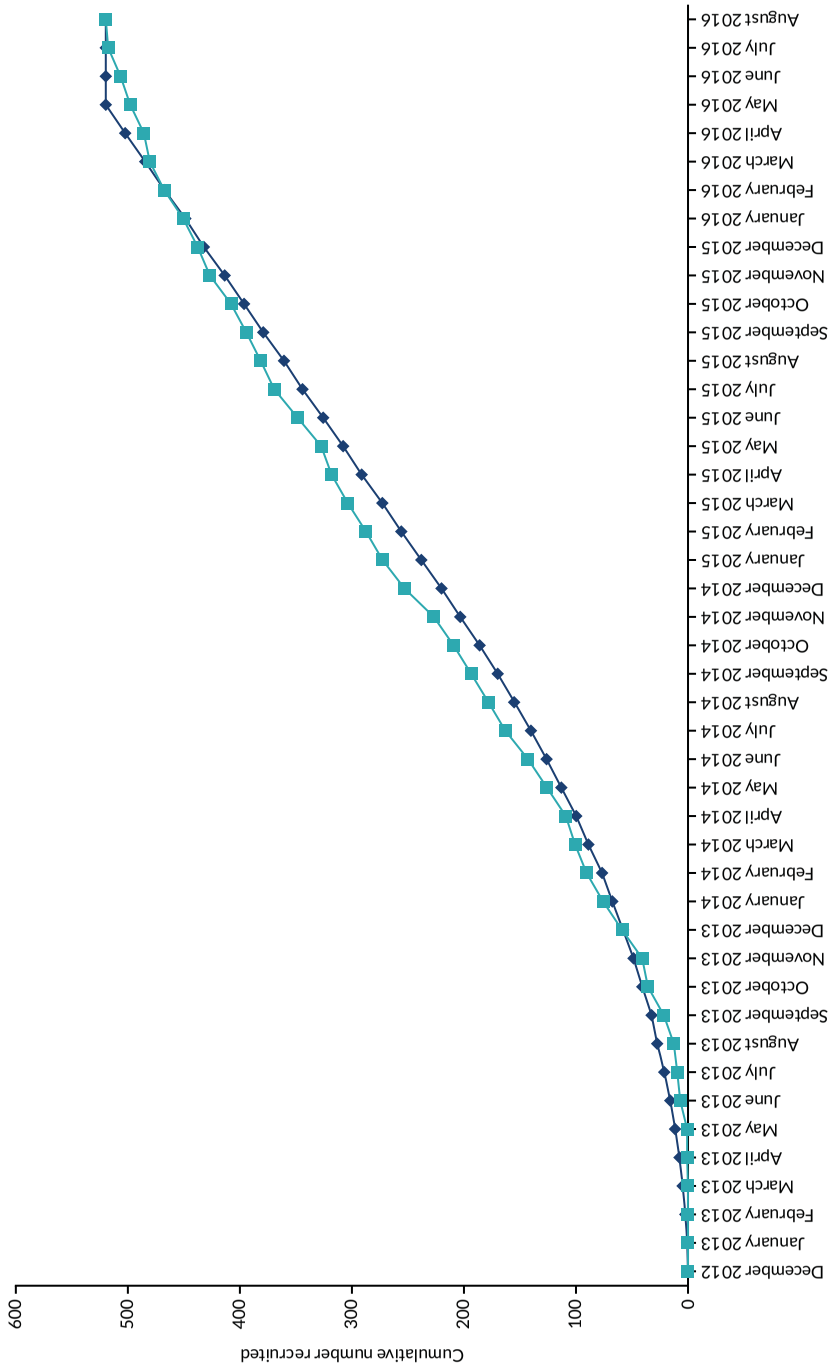
continued

TABLE 36 Details of pregnancies in the focal epilepsy trial (*continued*)

Patient ID	Day of pregnancy report[a]	Age at date of report (years)	Estimated day of delivery[a]	Day of delivery/ miscarriage[a]	Outcome	Randomised drug	Drug regimen when pregnancy reported
25	119	38	Missing	82	Miscarriage	Zonisamide	Levetiracetam, carbamazepine and topiramate
26	930	29	1168	1158	Normal postnatal examination	Zonisamide	Carbamazepine
27	538	26	785	780	Normal postnatal examination	Zonisamide	No anti-seizure medication
28	1252	30	1434	1362	Normal postnatal examination	Zonisamide	Levetiracetam
29	219	36	335	335	Normal postnatal examination	Zonisamide	Zonisamide
30	1099	28	1207	1188	Normal postnatal examination	Zonisamide	Zonisamide

a Day 0 = day of randomisation.

Additional tables and figures for the generalised and unclassified epilepsy trial



	December 2012	January 2013	February 2013	March 2013	April 2013	May 2013	June 2013	July 2013	August 2013	September 2013	October 2013	November 2013	December 2013	January 2014	February 2014	March 2014	April 2014	May 2014	June 2014	July 2014	August 2014	September 2014	October 2014	November 2014	December 2014	January 2015	February 2015	March 2015	April 2015	May 2015	June 2015	July 2015	August 2015	September 2015	October 2015	November 2015	December 2015	January 2016	February 2016	March 2016	April 2016	May 2016	June 2016	July 2016	August 2016
Arm B expected (*n*)	0	1	2	5	8	11	16	21	27	33	41	49	58	67	77	89	100	113	126	140	155	170	186	203	220	238	256	273	291	308	326	344	361	379	396	414	432	449	467	485	502	520	520	520	520
Arm B observed (*n*)	0	0	0	0	1	1	7	10	13	22	36	41	59	76	91	101	109	126	143	163	178	194	209	227	253	273	288	304	318	328	349	370	382	395	408	427	438	451	468	481	486	498	507	518	520
< 16 years (*n*)	0	0	0	0	1	1	6	7	8	12	20	24	34	42	50	55	57	66	75	88	95	105	113	126	142	155	164	173	180	187	199	215	224	232	239	253	257	266	273	281	284	295	303	311	312

FIGURE 25 Recruitment graph for the generalised and unclassified epilepsy trial.

Additional baseline tables and figures for generalised and unclassified trial

TABLE 37 Baseline characteristics

Characteristic	Valproate group	Levetiracetam group	Total
Age group (years), *n* (%)	260	260	520
5–7	52 (20.0)	48 (18.5)	100 (19.2)
8–11	54 (20.8)	56 (21.5)	110 (21.2)
12–15	54 (20.8)	48 (18.5)	102 (19.6)
16–29	70 (26.9)	81 (31.2)	151 (29.0)
≥ 30	30 (11.5)	27 (10.4)	57 (11.0)
Weight in kg (if aged ≤ 12 years) (*n*)	105	104	209
Mean (SD)	31 (11)	32 (12)	31 (11)
Median (IQR)	29 (23–36)	30 (24–37)	29 (23–37)
Range	15–66	16–81	15–81
Missing	16	12	28
EEG, *n* (%)			
EEG not done	20 (7.7)	24 (9.2)	44 (8.5)
EEG normal	58 (22.3)	51 (19.6)	109 (21.0)
Non-specific abnormality	11 (4.2)	9 (3.5)	20 (3.8)
Generalised abnormality: slow wave activity with spiking	138 (53.1)	133 (51.2)	271 (52.1)
Generalised abnormality: slow wave activity without spiking	8 (3.1)	7 (2.7)	15 (2.9)
Focal abnormality: paroxysmal slow activity with spiking	10 (3.8)	8 (3.1)	18 (3.5)
Focal abnormality: paroxysmal slow activity without spiking	2 (0.8)	7 (2.7)	9 (1.7)
Other	13 (5.0)	21 (8.1)	34 (6.5)
MRI, *n* (%)			
MRI not done	155 (59.6)	163 (62.7)	318 (61.2)
MRI normal	78 (30.0)	81 (31.2)	159 (30.6)
Head injury	0	0	0
Tumour	0	2 (0.8)	2 (0.4)
Cortical dysplasia	0	2 (0.8)	2 (0.4)
Hippocampal sclerosis	0	0	0
AVM or other vascular malformation (e.g. cavernoma)	2 (0.9)	1 (0.4)	3 (0.6)
Infarct	0	1 (0.4)	1 (0.2)
Haemorrhage	0	0	0
Previous infection (e.g. encephalitis/abscess)	0	0	0
Other	25 (9.7)	10 (3.9)	35 (6.8)

TABLE 37 Baseline characteristics (*continued*)

Characteristic	Valproate group	Levetiracetam group	Total
CT scan, *n* (%)			
CT scan not carried out	223 (85.8	216 (83.1)	439 (84.4)
CT scan normal	32 (12.3)	44 (16.9)	76 (14.6)
Head injury	0	0	0
Tumour	0	0	0
Cortical dysplasia	0	0	0
Hippocampal sclerosis	0	0	0
AVM or other vascular malformation (e.g. cavernoma)	0	0	0
Infarct	0	0	0
Haemorrhage	0	0	0
Previous infection (e.g. encephalitis/abscess)	0	0	0
Porencephalic cyst	0	0	0
Other	5 (1.9)	0	5 (1.0)

AVM, arteriovenous malformation.

TABLE 38 Completeness of follow-up statistics

Follow-up statistic	Valproate group	Levetiracetam group
Completeness of follow-up statistic	87.2%	82.6%
Maximum follow-up time (days)		
Median	1296	1293
IQR	1051.5–1523.5	1053.5–1516.5
Potential follow-up time (days)		
Median	494.5	730
IQR	366–928.5	397–1096
Actual follow-up time (days)		
Median	427	550
IQR	365–731	366–781
Reverse Kaplan–Meier estimate[a]		
Median	1096	1084
IQR	731–1461	730–1412
Number withdrawn or lost to follow-up[b]	23 (8.9%)	40 (15.4%)
Number lost to follow-up without treatment failure	12 (4.6%)	26 (10.0%)

a Reverse Kaplan–Meier estimates of follow-up time, with the censoring indicator reversed, so that being censored becomes the outcome of interest.
b Patient is considered lost to follow-up if they have not reached primary outcome, and their final follow-up is > 1 year before the end of the trial. The number includes formal withdrawals who also meet these criteria.

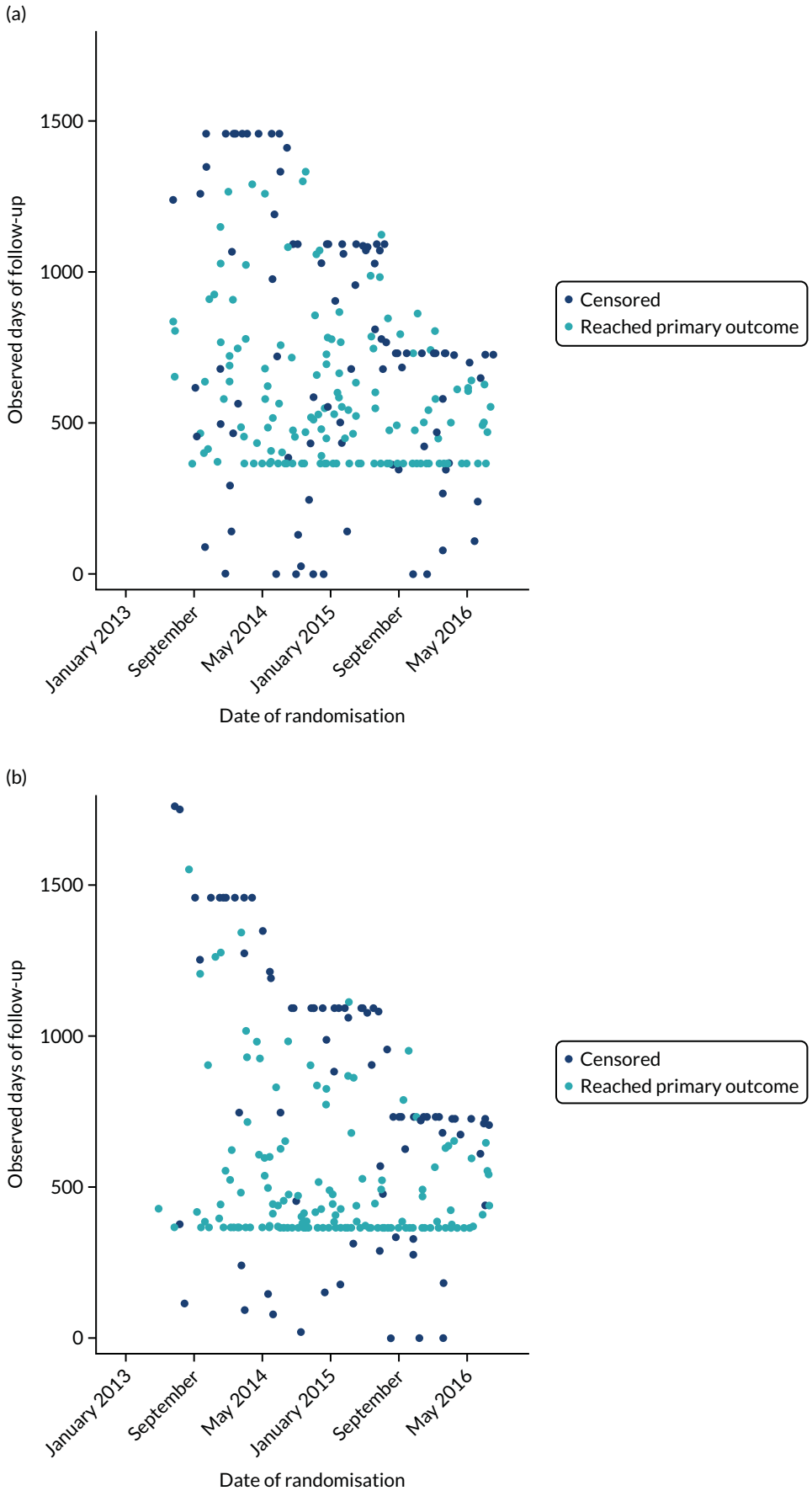


FIGURE 26 Completeness of follow-up scatterplots of observed follow-up time by date of randomisation: generalised and unclassified epilepsy trial. (a) Levetiracetam; and (b) valproate.

TABLE 39 Additional prespecified sensitivity analyses of primary outcome

Model and analysis set	Comparison	Time interval	HR (97.5% CI)
Alternative imputation rules	Valproate vs. levetiracetam	All follow-up	1.24 (1.01 to 1.51)
Misdiagnoses excluded (withdrawal reason 'not epilepsy')	Valproate vs. levetiracetam	All follow-up	1.18 (0.95 to 1.46)

TABLE 40 Adverse reactions by MedDRA-preferred term: levetiracetam vs. valproate for generalised or unclassified epilepsy

	Number of events		Number of patients (%)	
Event MedDRA-preferred term	Valproate group	Levetiracetam group	Valproate group ($n = 257$)	Levetiracetam group ($n = 258$)
Weight increased	27	8	26 (10.1)	8 (3.1)
Fatigue	16	16	14 (5.4)	15 (5.8)
Abnormal behaviour	8	21	8 (3.1)	18 (7.0)
Aggression	9	14	9 (3.5)	13 (5.0)
Headache	10	9	10 (3.9)	8 (3.1)
Increased appetite	14	4	14 (5.4)	4 (1.6)
Tremor	13	4	11 (4.3)	4 (1.6)
Nausea	10	6	9 (3.5)	6 (2.3)
Depressed mood	2	12	2 (0.8)	10 (3.9)
Anger	4	8	4 (1.6)	8 (3.1)
Depression	3	9	3 (1.2)	8 (3.1)
Somnolence	7	4	7 (2.7)	4 (1.6)
Alopecia	7	2	7 (2.7)	2 (0.8)
Decreased appetite	5	4	5 (1.9)	4 (1.6)
Lethargy	4	5	4 (1.6)	5 (1.9)
Insomnia	4	4	4 (1.6)	4 (1.6)
Memory impairment	5	3	5 (1.9)	3 (1.2)
Mood altered	3	5	3 (1.2)	5 (1.9)
Abdominal pain	5	2	5 (1.9)	2 (0.8)
Anxiety	1	6	1 (0.4)	5 (1.9)
Disturbance in attention	4	3	4 (1.6)	3 (1.2)
Dizziness	2	5	2 (0.8)	5 (1.9)
Irritability	2	5	2 (0.8)	5 (1.9)
Suicidal ideation	2	3	2 (0.8)	2 (0.8)
Vomiting	4	1	4 (1.6)	1 (0.4)
Weight decreased	2	3	2 (0.8)	3 (1.2)
Agitation	0	4	0	3 (1.2)
Cognitive disorder	2	2	2 (0.8)	2 (0.8)

continued

TABLE 40 Adverse reactions by MedDRA-preferred term: levetiracetam vs. valproate for generalised or unclassified epilepsy (*continued*)

Event MedDRA-preferred term	Number of events		Number of patients (%)	
	Valproate group	Levetiracetam group	Valproate group ($n = 257$)	Levetiracetam group ($n = 258$)
Enuresis	3	1	3 (1.2)	1 (0.4)
Psychomotor hyperactivity	2	2	2 (0.8)	2 (0.8)
Sedation	2	2	2 (0.8)	2 (0.8)
Sleep disorder	3	1	3 (1.2)	1 (0.4)
Amnesia	1	2	1 (0.4)	2 (0.8)
Diarrhoea	2	1	1 (0.4)	1 (0.4)
Tearfulness	0	3	0	3 (1.2)
Acne	2	0	2 (0.8)	0
Affect lability	2	0	2 (0.8)	0
Anal incontinence	0	2	0	1 (0.4)
Ataxia	2	0	1 (0.4)	0
Constipation	0	2	0	2 (0.8)
Dermatitis allergic	0	2	0	1 (0.4)
Diplopia	1	1	1 (0.4)	1 (0.4)
Emotional disorder	0	2	0	2 (0.8)
Gait disturbance	1	1	1 (0.4)	1 (0.4)
Migraine	1	1	1 (0.4)	1 (0.4)
Mood swings	0	2	0	2 (0.8)
Personality change	0	2	0	2 (0.8)
Rash	2	0	2 (0.8)	0
Abdominal pain upper	0	1	0	1 (0.4)
Abnormal dreams	0	1	0	1 (0.4)
Alanine aminotransferase increased	1	0	1 (0.4)	0
Apathy	0	1	0	1 (0.4)
Aphasia	0	1	0	1 (0.4)
Asthenia	1	0	1 (0.4)	0
Bicytopenia	1	0	1 (0.4)	0
Co-ordination abnormal	1	0	1 (0.4)	0
Defaecation urgency	1	0	1 (0.4)	0
Defiant behaviour	0	1	0	1 (0.4)
Disorientation	1	0	1 (0.4)	0
Distractibility	1	0	1 (0.4)	0
Drooling	1	0	1 (0.4)	0
Dysarthria	0	1	0	1 (0.4)
Dyspepsia	1	0	1 (0.4)	0
Dysphemia	0	1	0	1 (0.4)

TABLE 40 Adverse reactions by MedDRA-preferred term: levetiracetam vs. valproate for generalised or unclassified epilepsy (*continued*)

Event MedDRA-preferred term	Number of events		Number of patients (%)	
	Valproate group	Levetiracetam group	Valproate group ($n = 257$)	Levetiracetam group ($n = 258$)
Eating disorder	1	0	1 (0.4)	0
Encephalocele	0	1	0	1 (0.4)
Epistaxis	0	1	0	1 (0.4)
Erythema multiforme	0	1	0	1 (0.4)
Flatulence	0	1	0	1 (0.4)
Frustration tolerance decreased	0	1	0	1 (0.4)
Gastritis	1	0	1 (0.4)	0
Gingival bleeding	0	1	0	1 (0.4)
Gingival hypertrophy	0	1	0	1 (0.4)
Head banging	1	0	1 (0.4)	0
Hiccups	0	1	0	1 (0.4)
Hunger	1	0	1 (0.4)	0
Hypersensitivity	1	0	1 (0.4)	0
Intentional overdose	0	1	0	1 (0.4)
Intentional self-injury	0	1	0	1 (0.4)
Loss of libido	1	0	1 (0.4)	0
Mouth ulceration	0	1	0	1 (0.4)
Pancreatitis	0	1	0	1 (0.4)
Pancytopenia	0	1	0	1 (0.4)
Panic attack	1	0	1 (0.4)	0
Platelet count decreased	1	0	1 (0.4)	0
Poor-quality sleep	1	0	1 (0.4)	0
Restlessness	1	0	1 (0.4)	0
Seizure	0	1	0	1 (0.4)
Self-injurious ideation	1	0	1 (0.4)	0
Slow speech	0	1	0	1 (0.4)
Staring	0	1	0	1 (0.4)
Swelling face	0	1	0	1 (0.4)
Thirst	1	0	1 (0.4)	0
Total number of events and patients with at least one AR	220	223	96 (37.4)	107 (41.5)

TABLE 41 Serious ARs: generalised and unclassified epilepsy trial

Description	Seriousness	Severity	Suspect anti-seizure medication	Expectedness	Relationship: principal investigator assessment	Relationship: chief investigator assessment	Withdrawn from study drug	Outcome
Randomised to start treatment with valproate								
1: bicytopenia	Required hospitalisation	Mild	Valproate	Expected	Probably	Possibly	Yes	Ongoing at final follow-up
2: suicidal ideation	Required hospitalisation	Moderate	Valproate	Expected	Possibly	Unlikely	No	Resolved with sequelae
Randomised to start treatment with levetiracetam								
3: dizziness	Required hospitalisation	Moderate	Valproate	Expected	Unrelated	Probably	No	Resolved
			Lamotrigine	Expected	Probably	Probably	Yes	
4: intentional overdose	Required hospitalisation	Mild	Levetiracetam	Expected	Possibly	Unlikely	No	Resolved
5: suicidal ideation	Required hospitalisation	Moderate	Levetiracetam	Expected	Possibly	Possibly	No	Resolved with sequelae
6: pancreatitis	Required hospitalisation	Severe	Valproate	Expected	Almost certainly	Probably	Yes	Resolved

TABLE 42 Deaths in the generalised and unclassified epilepsy trial

Days from randomisation to death	Age at death (years)	Cause of death	Possibly related to trial treatments?
Randomised to start treatment with valproate			
1150	97	Ruptured aortic aneurysm	No
Randomised to start treatment with levetiracetam			
901	36	Sudden unexpected death in epilepsy	No

TABLE 43 Pregnancies in the generalised and unclassified epilepsy trial

Patient ID	Day of pregnancy report[a]	Age at date of report	Estimated day of delivery[a]	Day of delivery/ miscarriage[a]	Outcome	Randomised drug	Drug regimen when pregnancy reported
1	1113	21	1242	1237	Normal postnatal examination	Valproate	Levetiracetam
2	1001	17	1249	1252	Normal postnatal examination	Levetiracetam	Levetiracetam
2	1683	19	Missing	1647	Miscarriage	Levetiracetam	Levetiracetam
2	1737	19	Missing	1708	Miscarriage	Levetiracetam	Levetiracetam
3	195	17	340	321	Other	Levetiracetam	Levetiracetam
4	112	26	338	144	Miscarriage	Levetiracetam	Levetiracetam
4	274	26	465	469	Normal postnatal examination	Levetiracetam	Levetiracetam
4	1044	29	1245	1269	Major malformations	Levetiracetam	Carbamazepine
5	1107	22	1283	1271	Normal postnatal examination	Levetiracetam	Levetiracetam
6	686	26	903	891	Normal postnatal examination	Levetiracetam	Levetiracetam and pregabalin

a Day 0 = day of randomisation.

TABLE 44 Comparison of the characteristics of those who did and did not return QoL questionnaires

Characteristic	No return	Return	Total
Age (years) (*n*)	299	221	520
Mean (SD)	16.4 (8.8)	17.8 (15.9)	17.0 (12.3)
Median (IQR)	15.3 (9.5–21.2)	12.7 (8.3–18.2)	13.9 (8.9–19.7)
Range	5.0–48.8	5.0–94.4	5.0–94.4
Missing	0	0	0
Gender (*n*)	299	221	520
Male, *n* (%)	211 (70.6)	126 (57.0)	337 (64.8)
Female, *n* (%)	88 (29.4)	95 (43.0)	183 (35.2)
Learning disability (*n*)	299	221	520
Yes, *n* (%)	30 (10.0)	21 (9.5)	51 (9.8)
No, *n* (%)	269 (90.0)	200 (90.5)	469 (90.2)
Neurological deficit (*n*)	299	221	520
Yes, *n* (%)	9 (3.0)	7 (3.2)	16 (3.1)
No, *n* (%)	290 (97.0)	214 (96.8)	504 (96.9)
Previous or current neurological disorder, *n* (%)			
Stroke/cerebrovascular	0	0	0
Cerebral haemorrhage	0	2 (0.9)	2 (0.4)
Intracranial surgery	0	2 (0.9)	2 (0.4)
Head injury: post-traumatic amnesia for > 24 hours or a compound depressed fracture	2 (0.7)	0	2 (0.4)
Meningitis/encephalitis	3 (1.0)	1 (0.5)	4 (0.8)
Cortical dysplasia/developmental anomaly	0	0	0
Other	12 (4.0)	12 (5.4)	24 (4.6)
History, *n* (%)			
Febrile convulsions	29 (9.7)	15 (6.8)	44 (8.5)
Any other acute symptomatic seizures	8 (2.7)	6 (2.7)	14 (2.7)
Family history of epilepsy in primary relatives	57 (19.1)	42 (19.0)	99 (19.0)
Epilepsy type (*n*)	299	221	520
Generalised epilepsy, *n* (%)	218 (72.9)	179 (81.0)	397 (76.3)
Unclassified epilepsy, *n* (%)	81 (27.1)	42 (19.0)	123 (23.7)
Epilepsy syndrome (generalised epilepsy only), *n* (%)			
Childhood absence	54 (24.8)	50 (27.9)	104 (26.2)
Juvenile absence	14 (6.4)	22 (12.3)	36 (9.1)
Juvenile myoclonic	37 (17.0)	14 (7.8)	51 (12.8)
Epilepsy with tonic–clonic seizures on awakening	12 (5.5)	11 (6.1)	23 (5.8)
Other idiopathic generalised epilepsy not specified	104 (47.7)	76 (42.5)	180 (45.3)
Other epilepsy syndrome	7 (3.2)	10 (5.6)	17 (4.3)

Appendix 4 Additional tables and figures for the health economic analysis

TABLE 45 Unit costs relating to self-reported resource use

Item of resource	Unit cost (child)	Assumption	Reference
GP consultation at GP surgery	£39.00	9.22 minutes	55
Nurse consultation at GP surgery	£10.85	15.5 minutes	55,85
GP home visit	£99.45	11.4 minutes, 12 minutes' travel	55,85
Nurse home visit	£40.00	N02AF	54
Doctor at hospital	£185.00	Adult: service 400	54
	(£203.00)	Child: service 223	
Nurse at hospital	£29.19	15.5 minutes	55
Hospital overnight	£589.00	Non-elective stay	54
Ambulance	£257.00	ASS02	54
A&E visit	£192.18	(T01A, T01NA)[a]	54
Blood test	£3.00	DAPS05	54
Urine test	£2.00	DAPS	54
Ultrasound	£54.82	(RD40Z, RD41Z, RD42Z, RD43Z)[a]	54
Radiography	£31.00	DAPF	54
CT scan	£88.53	Adult: (RD20A, RD21A)[a]	54
	(£99.74)	Child: (RD20B, RD21B)[a]	
MRI scan	£138.24	Adult: (RD01A, RD02A)[a]	54
	(£141.87)	Child: (RD01B, RD02B)[a]	
EEG	£199.00	Adult: AA33C	54
	(£340.00)	Child: AA33D	
Health visitor	£72.00	N03G	54
Social worker	£50.00	1-hour visit	55
	(£51.00)		
Occupational therapist	£83.00	Adult: A06A1	54
	(£141.00)	Child: A06C1	
Psychologist	£199.00	Service 656	54
Counsellor	£45.00	1-hour visit	55
	(£94.00)		
Physiotherapist	£63.00	Adult: A08A1	54
	(£101.00)	Child: A08C1	

continued

TABLE 45 Unit costs relating to self-reported resource use (*continued*)

Item of resource	Unit cost (child)	Assumption	Reference
Resources identified from free text			
Telephone consultation (GP)	£15.52		55
GP out of hours	£72.97	Inflated to 2018/19	86
MMR	£7.64	In addition to nurse appointment	24
Pharmacist	£11.00	Band 6, 15 minutes	55
Repeat prescription	£7.30		55
Stool test	£2.00	DAPS	54
MRSA swab/saliva test	£8.00	DAPS07	54
Psychiatrist	£226.00	Adult: Service 713	54
	(£227.00)	Child: Service 711	
(Family) support worker	£24.00		55
Speech therapist	£107.00	Adult: A13A1	54
	(£100.00)	Child: A13C1	
Dietitian	£90.00	A03	54
Sexual health specialist	£92.00		55
Podiatrist	£43.00	A09A	54
Podiatrist minor surgery	£86.00	A09B	54
Midwife	£58.00	N01A	54
Assistive technology team	£123.00	NCRT	54
Hearing test	£101.00	Adult: CA37A	54
	(£89.00)	Child: CA37B	
Optician	£76.00	Service 662	54
NHS glasses	£39.10	Voucher A	87
Dentist	£98.00	M01B	54
Hygienist	£17.00	30-minute visit	55
Orthodontist	£121.00	Service 143	54
CAMHS	(£221.00)	CAMHSCC	54
School nurse/SENCO	(£68.00)	N05CO	54
Mammogram	£57.37	Inflated to 2018/19	88
Cervical smear	£39.76	Inflated to 2018/19	89
NHS Direct	£13.02	Inflated to 2018/19	90
Anticoagulant service	£37.00	Service 324	54
Radiofrequency for pain management	£699.00	AB15Z	54
Radiotherapy	£182.00	SC31Z	54
Venesection	£4.00	DAPS08	54
ECG	£72.57	Adult: RD51A	54
	(£53.58)	Child: RD51B	

TABLE 45 Unit costs relating to self-reported resource use (*continued*)

Item of resource	Unit cost (child)	Assumption	Reference
Video telemetry/long-term EEG monitoring	£491.00	AA81Z	54
Cerebral angiography/contrast fluoroscopy	£170.00	RD31Z	54
Spinal fluid test	£617.00	Adult: HC72A	54
	(£882.00)	Child: HC72B	
Cystoscopy	£250.00	Adult: LB72A	54
	(£849.00)	Child: LB72B	
Colonoscopy	£520.00	FE32Z	54
Sigmoidoscopy	£386.00	FE35Z	54
Endoscopy	£454.00	FE22Z	54
Dual X-ray absorptiometry	£71.92	RD50Z	54
PET scan	£506.00	Adult: RN01A	54
	(£389.00)	Child: RN01B	
Peak flow test	£152.00	DZ45Z	54
Field exercise test	£55.00	DZ32Z	54
Cataract operation	£915.00	BZ34C	54
Orthotics	£124.00	Service 658	54
Intermediate sinus procedures	£2344.00	CA28Z	54
Insertion of grommets	£998.00	CA35B	54
Arm fracture and CC	£1417.00	HE51G	54
Rib fracture	£1025.00	HE71D	54
Hand fracture	£384.00	HE41D	54
Minor dental procedures in those aged < 19	£153.00	CD03B	54
Tooth extraction in those aged ≤ 18 years	£491.00	CD07B	54
Minor skin procedures	£215.00	Adult: JC43C	54
	(£288.00)	Child: JC43D	
Diabetic retinopathy screen	£108.00	BZ88A	54
Nasal polypectomy	£1715.00	CA14Z	54
Skin biopsy external nose	£461.00	CA16Z	54
Percutaneous biopsy	£1491.00	YH32A	54
Liver biopsy	£671.00	YG11A	54
Biopsy of prostate	£504.00	LB76Z	54
Sleep apnoea test	£309.00	DZ50Z	54
Pelvis fracture (hip fracture)	£2117.00	HE11H	54
Vaginal tape operation for urinary incontinence	£2020.00	LB51B	54

continued

TABLE 45 Unit costs relating to self-reported resource use (*continued*)

Item of resource	Unit cost (child)	Assumption	Reference
Minor foot operation	£832.00	Adult: HN35A	54
	(£580.00)	Child: HN35B	
Hernia repair	£2651.00	FF60D	54
Hysterectomy	£3515.00	MA08B	54
Triple heart bypass	£10,199.00	ED28B	54
Hip replacement	£6057.00	HN12F	54
Pacemaker fitted	£1085.00	EY08E	54
Implantation of loop recorder	£1270.00	EY12B	54
Removal of loop recorder	£693.00	EY13Z	54
Cholecystectomy (gall bladder removal)	£2861.00	GA10K	54
Knee replacement	£5699.00	HN22E	54
Reconstructive surgery (chest clinic)	£5706.00	JA30Z	54
Cardiac catheterisation	£1142.00	EY43F	54
Walk-in centre visit	£72.07	(T02A, T02NA, T03A, T03NA, T04A and T04NA)[a]	54
See and treat (no convey)	£209.00	ASS01	54

CAMHS, Child and Adolescent Mental Health Services; CC, complication or comorbidity; ECG, electrocardiography; PET, positron emission tomography; SENCO, special educational needs co-ordinator.
a Weighted average of codes.

TABLE 46 Unit costs relating to the most commonly reported HRGs at baseline and at the 24-month time horizon

HRG code	Description	Elective	NEL	NES	Day case
Admitted patient care					
AA26G	Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head injury, with a CC score of 3–5	£3051	£1924	£416	£549
AA26H	Muscular, balance, cranial or peripheral nerve disorders, epilepsy or head injury, with a CC score of 0–2	£2358	£1713	£357	£595
AA33C	Conventional EEG, EMG or nerve conduction studies, 19 years and over	£1952	£2993	£827	£807
AA80Z	Complex long-term EEG monitoring	£2126	£2960	£1182	£901
PR02B	Paediatric epilepsy syndrome with a CC score of 1–5	£2835	£3242	£602	£998
PR02C	Paediatric epilepsy syndrome with a CC score of 0	£1800	£2741	£564	£742
SB97Z	Same-day chemotherapy admission or attendance	£308	£3014	£382	£110
SC97Z	Same-day radiotherapy admission or attendance (excluding brachytherapy)	£972	–	£287	£1389
WH04E	Poisoning diagnosis without interventions, with a CC score of 0 or 1	£1176	£1347	£383	£362
WH50B	Procedure not carried out, for other or unspecified reasons	£578	£1995	£477	£330
WJ11Z	Other disorders of immunity	£759	£3258	£454	£437

TABLE 46 Unit costs relating to the most commonly reported HRGs at baseline and at the 24-month time horizon (*continued*)

Service		Currency		Consultation	Procedure
Outpatients					
110	Trauma and orthopaedics	WF01A	Non-admitted face-to-face attendance, follow-up	£120	£245
110	Trauma and orthopaedics	N/A	N/A	£120	N/A
223	Paediatric epilepsy	N/A	N/A	£203	N/A
291	Paediatric neuro-disability	N/A	N/A	£251	N/A
320	Cardiology	WF01A	Non-admitted face-to-face attendance, follow-up	£139	£193
400	Neurology	WF01A	Non-admitted face-to-face attendance, follow-up	£177	£697
400	Neurology	WF01B	Non-admitted face-to-face attendance, first	£177	£410
400	Neurology	N/A	N/A	£177	N/A
420	Paediatrics	WF01A	Non-admitted face-to-face attendance, follow-up	£217	£889
420	Paediatrics	WF01B	Non-admitted face-to-face attendance, first	£217	£321
420	Paediatrics	N/A	N/A	£217	N/A
421	Paediatric neurology	WF01A	Non-admitted face-to-face attendance, follow-up	£339	£1099
421	Paediatric neurology	N/A	N/A	£339	N/A
650	Physiotherapy	WF01A	Non-admitted face-to-face attendance, follow-up	£58	£80
Service		**Currency**			
A&E					
N/A	N/A	ASS02	See and treat and convey	£257	
T01A	Type 01 admitted	VB04Z	Emergency medicine, category 2 investigation with category 4 treatment	£318	
T01A	Type 01 admitted	VB07Z	Emergency medicine, category 2 investigation with category 2 treatment	£251	
T01A	Type 01 admitted	VB08Z	Emergency medicine, category 2 investigation with category 1 treatment	£220	
T01A	Type 01 admitted	VB09Z	Emergency medicine, category 1 investigation with category 1 or 2 treatment	£159	
T01NA	Type 01 non-admitted	VB07Z	Emergency medicine, category 2 investigation with category 2 treatment	£200	

continued

TABLE 46 Unit costs relating to the most commonly reported HRGs at baseline and at the 24-month time horizon (*continued*)

Service		Currency		
T01NA	Type 01 non-admitted	VB08Z	Emergency medicine, category 2 investigation with category 1 treatment	£179
T01NA	Type 01 non-admitted	VB09Z	Emergency medicine, category 1 investigation with category 1 or 2 treatment	£133
T01NA	Type 01 non-admitted	VB11Z	Emergency medicine, no investigation with no significant treatment	£114
T03NA	Type 03 non-admitted	VB07Z	Emergency medicine, category 2 investigation with category 2 treatment	£110
T03NA	Type 03 non-admitted	VB09Z	Emergency medicine, category 1 investigation with category 1 or 2 treatment	£68
T04NA	Type 04 non-admitted	VB09Z	Emergency medicine, category 1 investigation with category 1 or 2 treatment	£53

CC, complication or comorbidity; EMG, electromyogram; N/A, not applicable; NEL, non-elective long stay; NES, non-elective short stay.

TABLE 47 Unit costs relating to trial anti-seizure medicines

Formulation	Strength	*N*/volume	Unit cost (£)
Lamotrigine			
Dispersible tablet	2 mg	30	18.81
Dispersible tablet	5 mg	28	7.67
Dispersible tablet	25 mg	56	4.70
Dispersible tablet	100 mg	56	6.29
Tablet	25 mg	56	1.89
Tablet	50 mg	56	2.46
Tablet	100 mg	56	3.48
Tablet	200 mg	56	4.37
Levetiracetam			
Tablet	250 mg	60	5.72
Tablet	500 mg	60	9.97
Tablet	750 mg	60	8.96
Tablet	1 g	60	14.97
Oral solution, sugar free	100 mg/ml	300	7.71

TABLE 47 Unit costs relating to trial anti-seizure medicines (*continued*)

Formulation	Strength	*N*/volume	Unit cost (£)
Valproate			
Gastroresistant tablet	200 mg	100	10.56
Gastroresistant tablet	500 mg	100	25.44
Modified-release capsule	300 mg	100	13.00
Modified-release granules	250 mg	30	30.00
Modified-release granules [sodium valproate (Epilim®, Sanofi SA)]	1000 mg	30	30.00
Modified-release granules [sodium valproate (Episenta®, Desitin Pharma Ltd, Atterbury, UK)]	1000 mg	100	41.00
Modified-release tablet	200 mg	30	3.50
Modified-release tablet	300 mg	30	5.24
Modified-release tablet	500 mg	30	8.73
Oral solution, sugar free	40 mg/ml	300	10.64
Zonisamide			
Capsule	25 mg	14	7.55
Capsule	50 mg	56	40.01
Capsule	100 mg	56	5.27

TABLE 48 Summary of data completeness by outcome, time point and treatment group: focal epilepsy

		Lamotrigine group (number of participants)			Levetiracetam group (number of participants)			Zonisamide group (number of participants)		
Variable	Time point	Complete	Incomplete	Total	Complete	Incomplete	Total	Complete	Incomplete	Total
Participants										
Admitted patient care	Baseline	266	64	330	261	71	332	245	83	328
Outpatients	Baseline	266	64	330	261	71	332	245	83	328
A&E	Baseline	266	64	330	261	71	332	245	83	328
Primary care	3 months	182	148	330	186	146	332	182	146	328
Community care	3 months	182	148	330	186	146	332	182	146	328
Concomitant medication	3 months	182	148	330	186	146	332	182	146	328
Primary care	6 months	177	153	330	176	156	332	174	154	328
Community care	6 months	177	153	330	176	156	332	174	154	328
Concomitant medication	6 months	177	153	330	176	156	332	174	154	328
Primary care	12 months	156	174	330	154	178	332	155	173	328
Community care	12 months	156	174	330	154	178	332	155	173	328
Admitted patient care	12 months	298	34	330	286	47	332	272	56	328
Outpatients	12 months	298	34	330	286	47	332	272	56	328
A&E	12 months	298	34	330	286	47	332	272	56	328
Anti-seizure medication	12 months	291	39	330	293	39	332	280	48	328
Concomitant medication	12 months	156	174	330	154	178	332	155	173	328
Primary care	24 months	135	195	330	133	199	332	130	198	328
Community care	24 months	135	195	330	133	199	332	130	198	328
Admitted patient care	24 months	299	32	330	291	43	332	280	48	328
Outpatients	24 months	299	32	330	291	43	332	280	48	328
A&E	24 months	299	32	330	291	43	332	280	48	328

Variable	Time point	Lamotrigine group (number of participants)			Levetiracetam group (number of participants)			Zonisamide group (number of participants)		
		Complete	Incomplete	Total	Complete	Incomplete	Total	Complete	Incomplete	Total
Anti-seizure medication	24 months	257	73	330	260	72	332	239	89	328
Concomitant medication	24 months	135	195	330	133	199	332	130	198	328
Primary care	36 months	93	175	268	92	174	266	84	183	267
Community care	36 months	93	175	268	92	174	266	84	183	267
Admitted patient care	36 months	236	32	268	225	41	266	217	50	267
Outpatients	36 months	236	32	268	225	41	266	217	50	267
A&E	36 months	236	32	268	225	41	266	217	50	267
Anti-seizure medication	36 months	125	143	268	134	132	266	118	149	267
Concomitant medication	36 months	93	175	268	92	174	266	84	183	267
Primary care	48 months	46	125	171	58	117	175	44	130	174
Community care	48 months	46	125	171	58	117	175	44	130	174
Admitted patient care	48 months	150	21	171	151	24	175	141	33	174
Outpatients	48 months	150	21	171	151	24	175	141	33	174
A&E	48 months	150	21	171	151	24	175	141	33	174
Anti-seizure medication	48 months	62	109	171	66	109	175	52	122	174
Concomitant medication	48 months	46	125	171	58	117	175	44	130	174
Primary care	60 months	26	54	80	29	50	79	24	53	77
Community care	60 months	26	54	80	29	50	79	24	53	77
Admitted patient care	60 months	74	6	80	69	10	79	59	18	77
Outpatients	60 months	74	6	80	69	10	79	59	18	77
A&E	60 months	74	6	80	69	10	79	59	18	77
Anti-seizure medication	60 months	19	61	80	22	57	80	16	61	80
Concomitant medication	60 months	26	54	80	29	50	79	24	53	77

continued

TABLE 48 Summary of data completeness by outcome, time point and treatment group: focal epilepsy (*continued*)

		Lamotrigine group (number of participants)			Levetiracetam group (number of participants)			Zonisamide group (number of participants)		
Variable	Time point	Complete	Incomplete	Total	Complete	Incomplete	Total	Complete	Incomplete	Total
Utilities										
EQ-5D	Baseline	209	121	330	202	130	332	205	123	328
NEWQOL-6D	Baseline	201	129	330	190	142	332	186	142	328
EQ-VAS	Baseline	188	142	330	187	145	332	190	138	328
EQ-5D	12 months	148	182	330	148	184	332	147	181	328
NEWQOL-6D	12 months	107	223	330	100	232	332	104	224	328
EQ-VAS	12 months	135	194	330	126	206	332	136	192	328
EQ-5D	24 months	121	209	330	124	208	332	122	206	328
NEWQOL-6D	24 months	87	243	330	88	244	332	80	248	328
EQ-VAS	24 months	116	214	330	111	221	332	114	214	328
EQ-5D	36 months	94	174	268	93	173	266	83	184	267
NEWQOL-6D	36 months	69	199	268	58	208	266	61	206	267
EQ-VAS	36 months	93	175	268	89	177	266	78	189	267
EQ-5D	48 months	50	121	171	58	117	175	46	128	174
NEWQOL-6D	48 months	37	134	171	41	134	175	33	141	174
EQ-VAS	48 months	48	123	171	55	120	175	43	131	174
EQ-5D	60 months	31	49	80	31	48	79	26	51	77
NEWQOL-6D	60 months	25	55	80	16	63	79	17	60	77
EQ-VAS	60 months	31	49	80	30	49	79	25	52	77

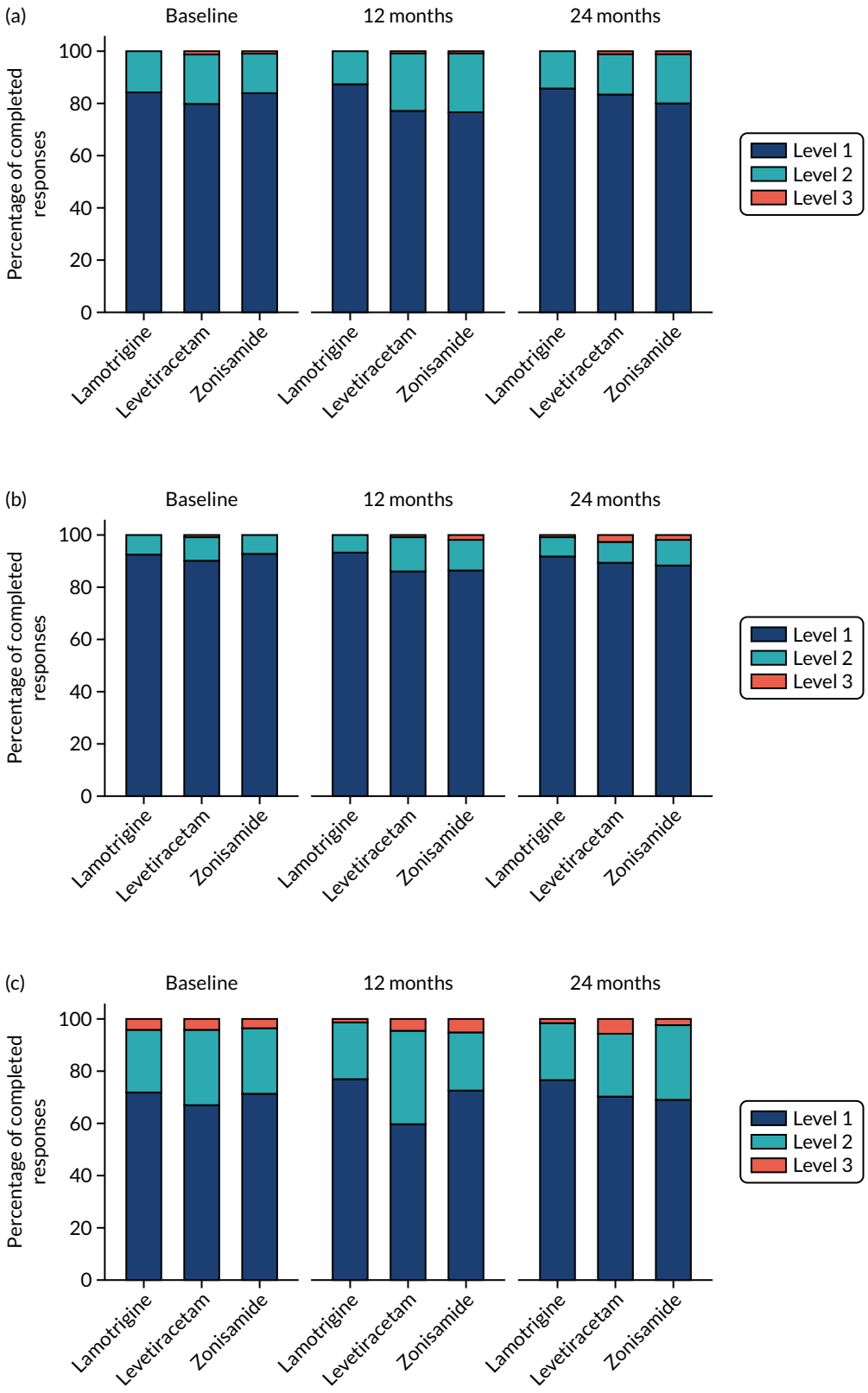


FIGURE 27 Distribution of participants' responses to each EQ-5D attribute by treatment allocated and time: focal epilepsy. Levels range from 1 to 3, with 3 representing the most severe problem. (a) Mobility; (b) self-care; (c) usual activities; (d) pain or discomfort; and (e) anxiety or depression. (*continued*)

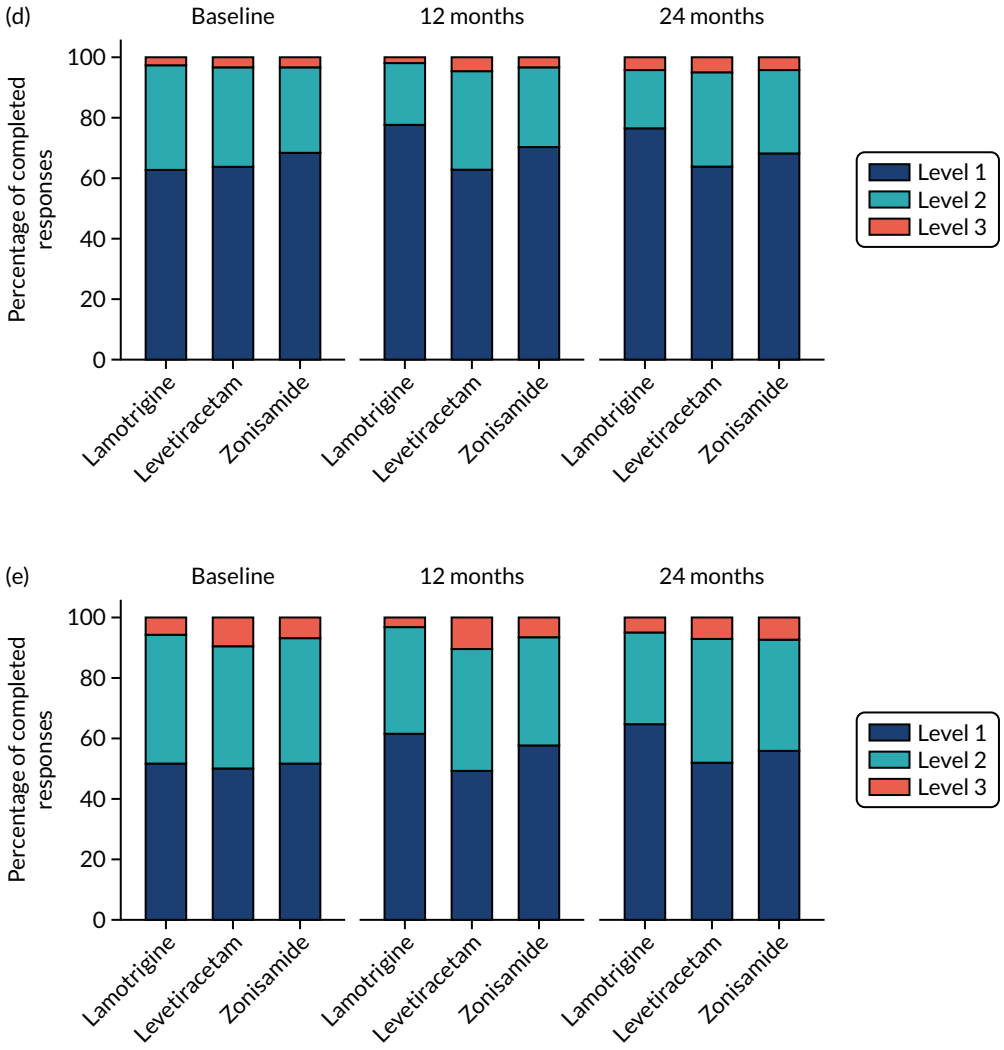


FIGURE 27 Distribution of participants' responses to each EQ-5D attribute by treatment allocated and time: focal epilepsy. Levels range from 1 to 3, with 3 representing the most severe problem. (a) Mobility; (b) self-care; (c) usual activities; (d) pain or discomfort; and (e) anxiety or depression.

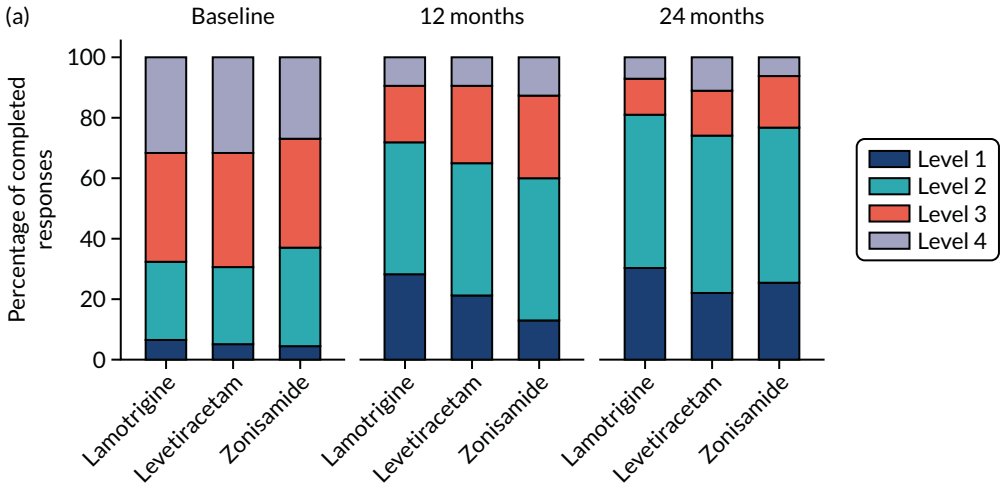


FIGURE 28 Distribution of participants' responses to each NEWQOL-6D attribute by treatment allocated and time: focal epilepsy. Levels range from 1 to 4, with 4 representing the most severe problem. (a) Worry; (b) depression; (c) memory; (d) concentration; (e) control; and (f) stigma. (*continued*)

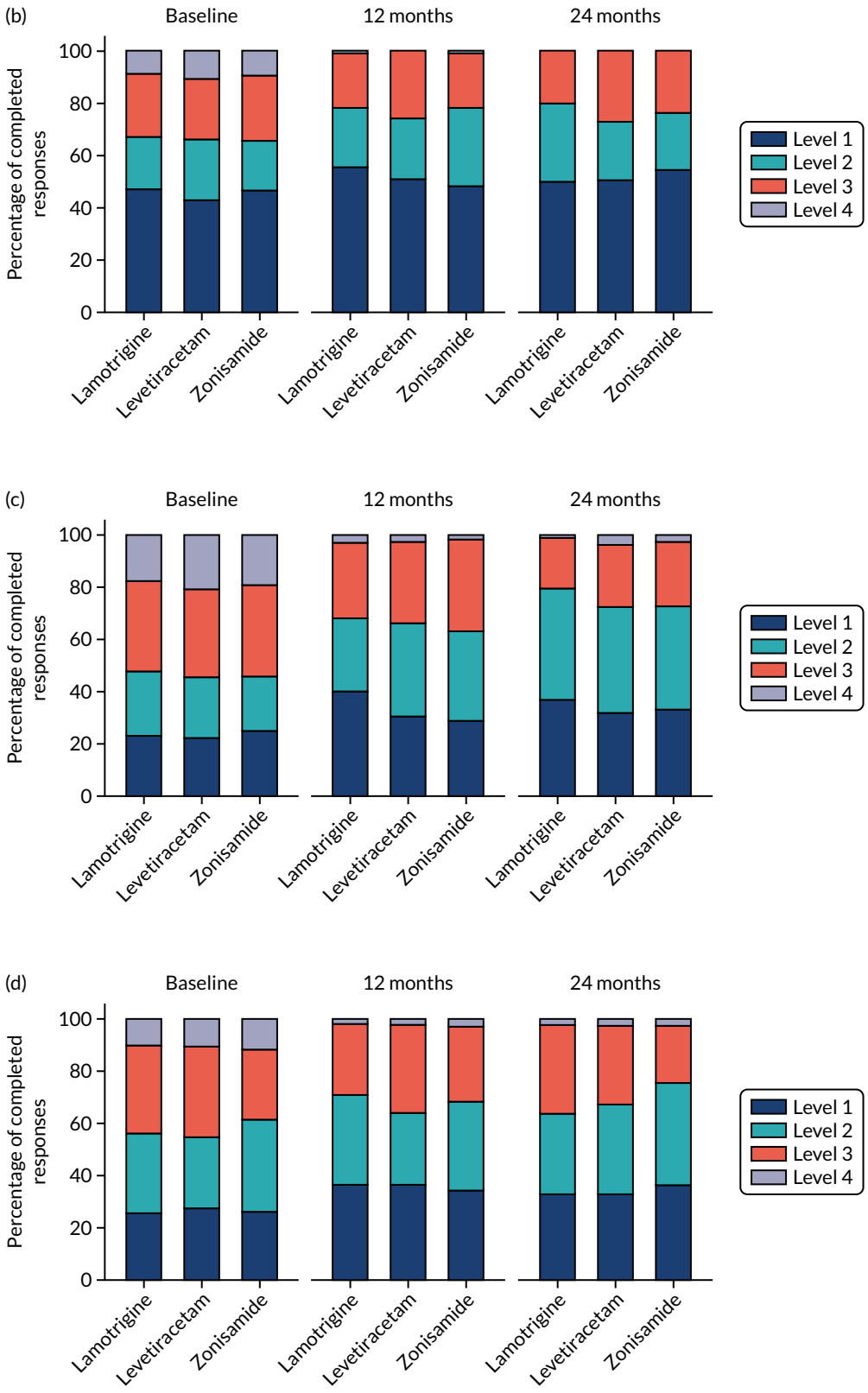


FIGURE 28 Distribution of participants' responses to each NEWQOL-6D attribute by treatment allocated and time: focal epilepsy. Levels range from 1 to 4, with 4 representing the most severe problem. (a) Worry; (b) depression; (c) memory; (d) concentration; (e) control; and (f) stigma. (*continued*)

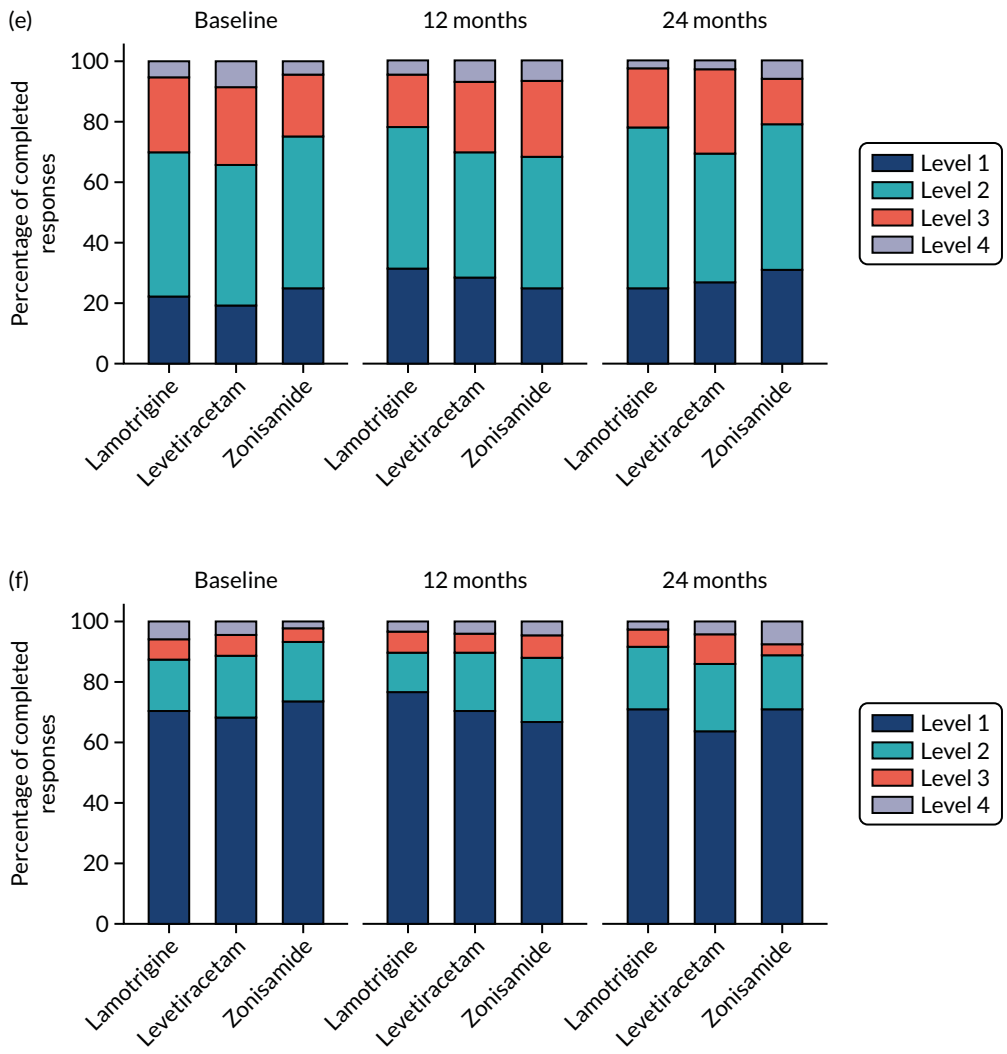


FIGURE 28 Distribution of participants' responses to each NEWQOL-6D attribute by treatment allocated and time: focal epilepsy. Levels range from 1 to 4, with 4 representing the most severe problem. (a) Worry; (b) depression; (c) memory; (d) concentration; (e) control; and (f) stigma.

TABLE 49 Summary of data completeness by outcome, time point and treatment group: generalised and unclassified epilepsy

		Valproate group (number of participants)			Levetiracetam group (number of participants)		
Variable	**Time point**	**Complete**	**Incomplete**	**Total**	**Complete**	**Incomplete**	**Total**
Participants							
Admitted patient care	Baseline	202	58	260	210	50	260
Outpatients	Baseline	202	58	260	210	50	260
A&E	Baseline	202	58	260	210	50	260
Primary care	3 months	128	132	260	115	145	260
Community care	3 months	128	132	260	115	145	260
Concomitant medication	3 months	128	132	260	115	145	260
Primary care	6 months	118	142	260	94	166	260
Community care	6 months	118	142	260	94	166	260
Concomitant medication	6 months	118	142	260	94	166	260

TABLE 49 Summary of data completeness by outcome, time point and treatment group: generalised and unclassified epilepsy (*continued*)

		Valproate group (number of participants)			Levetiracetam group (number of participants)		
Variable	Time point	Complete	Incomplete	Total	Complete	Incomplete	Total
Primary care	12 months	99	161	260	86	174	260
Community care	12 months	99	161	260	86	174	260
Admitted patient care	12 months	218	42	260	221	39	260
Outpatients	12 months	218	42	260	221	39	260
A&E	12 months	218	42	260	221	39	260
Anti-seizure medication	12 months	234	26	260	230	30	260
Concomitant medication	12 months	99	161	260	86	174	260
Primary care	24 months	73	187	260	75	185	260
Community care	24 months	73	187	260	75	185	260
Admitted patient care	24 months	224	36	260	223	37	260
Outpatients	24 months	224	36	260	223	37	260
A&E	24 months	224	36	260	223	37	260
Anti-seizure medication	24 months	206	54	260	185	75	260
Concomitant medication	24 months	73	187	260	75	185	260
Primary care	36 months	52	139	191	50	139	189
Community care	36 months	52	139	191	50	139	189
Admitted patient care	36 months	160	31	191	158	31	189
Outpatients	36 months	160	31	191	158	31	189
A&E	36 months	160	31	191	158	31	189
Anti-seizure medication	36 months	86	105	191	82	107	189
Concomitant medication	36 months	52	139	191	49	140	189
Primary care	48 months	23	61	84	19	64	83
Community care	48 months	23	61	84	19	64	83
Admitted patient care	48 months	69	15	84	66	17	83
Outpatients	48 months	69	15	84	66	17	83
A&E	48 months	69	15	84	66	17	83
Anti-seizure medication	48 months	27	57	84	23	60	83
Concomitant medication	48 months	22	62	84	19	64	83
Primary care	60 months	5	3	8	4	3	7
Community care	60 months	5	3	8	4	3	7
Admitted patient care	60 months	8	0	8	5	2	7
Outpatients	60 months	8	0	8	5	2	7
A&E	60 months	8	0	8	5	2	7
Anti-seizure medication	60 months	0	8	8	0	7	7
Concomitant medication	60 months	5	3	8	4	3	7

continued

TABLE 49 Summary of data completeness by outcome, time point and treatment group: generalised and unclassified epilepsy (*continued*)

Variable	Time point	Valproate group (number of participants)			Levetiracetam group (number of participants)		
		Complete	Incomplete	Total	Complete	Incomplete	Total
Utilities							
EQ-5D	Baseline	145	115	260	129	131	260
NEWQOL-6D	Baseline	101	159	260	85	175	260
EQ-VAS	Baseline	139	121	260	132	128	260
EQ-5D	12 months	98	162	260	83	177	260
NEWQOL-6D	12 months	55	205	260	44	216	260
EQ-VAS	12 months	89	171	260	73	187	260
EQ-5D	24 months	72	188	260	73	187	260
NEWQOL-6D	24 months	33	227	260	34	226	260
EQ-VAS	24 months	68	192	260	63	197	260
EQ-5D	36 months	52	139	191	49	140	189
NEWQOL-6D	36 months	32	159	191	30	159	189
EQ-VAS	36 months	48	143	191	43	146	189
EQ-5D	48 months	23	61	84	19	64	83
NEWQOL-6D	48 months	14	70	84	13	70	83
EQ-VAS	48 months	21	63	84	16	67	83
EQ-5D	60 months	5	3	8	4	3	7
NEWQOL-6D	60 months	4	5	8	1	6	7
EQ-VAS	60 months	5	3	8	4	3	7

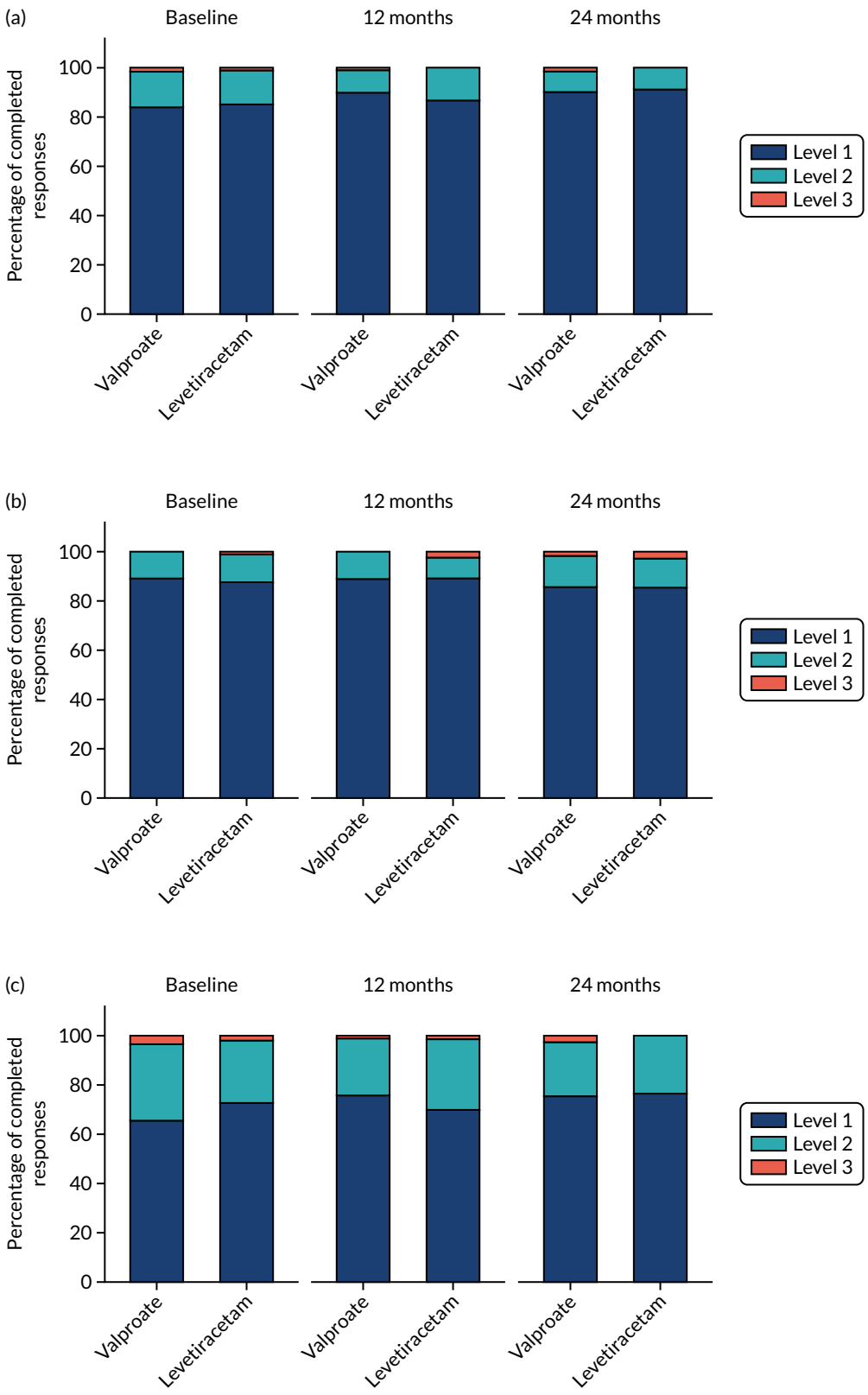


FIGURE 29 Distribution of participants' responses to each EQ-5D attribute by treatment allocated and time: generalised and unclassified epilepsy. For presentation purposes, visits within 90 days of the intended visit date are included. Levels range from 1 to 3, with 3 representing the most severe problem. The percentage of completed responses (%) are reported by intervention group. (a) Mobility; (b) self-care; (c) usual activities; (d) pain or discomfort; and (e) anxiety or depression. (*continued*)

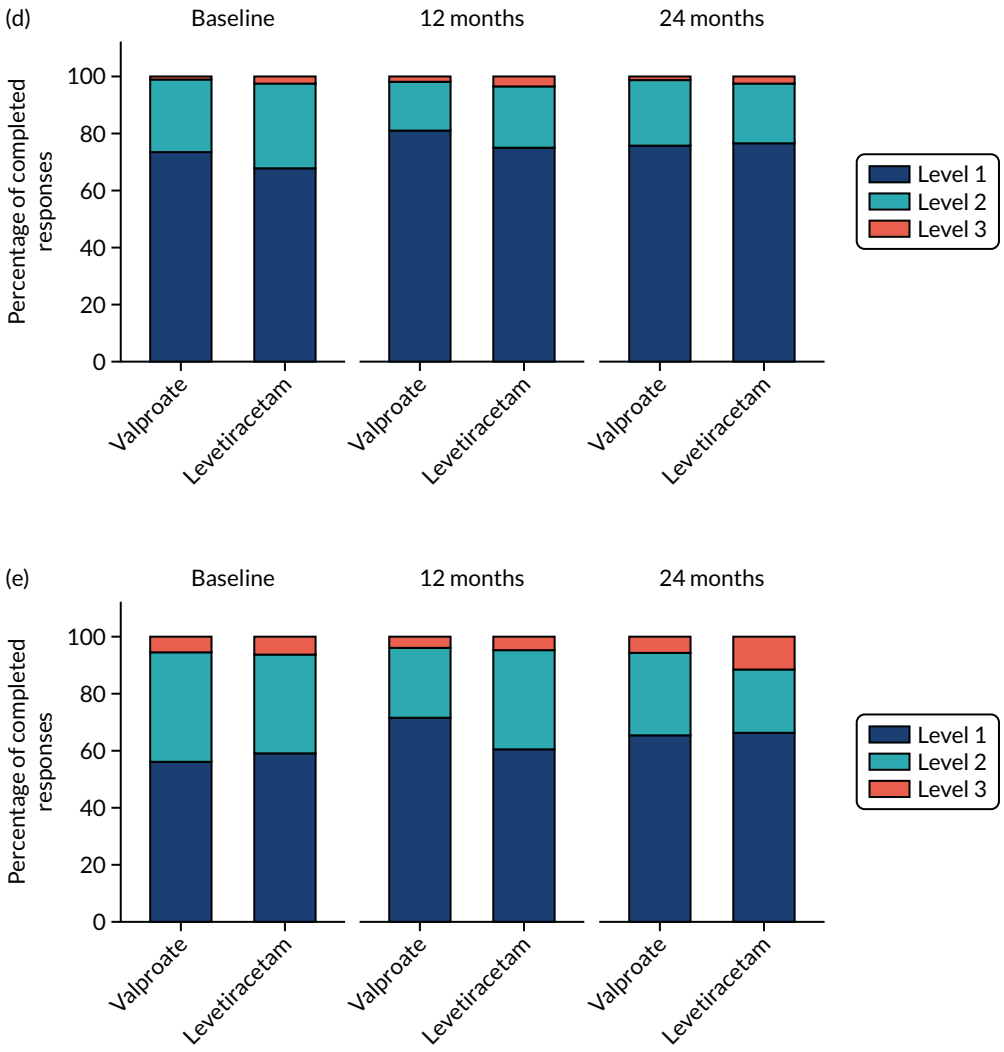


FIGURE 29 Distribution of participants' responses to each EQ-5D attribute by treatment allocated and time: generalised and unclassified epilepsy. For presentation purposes, visits within 90 days of the intended visit date are included. Levels range from 1 to 3, with 3 representing the most severe problem. The percentage of completed responses (%) are reported by intervention group. (a) Mobility; (b) self-care; (c) usual activities; (d) pain or discomfort; and (e) anxiety or depression.

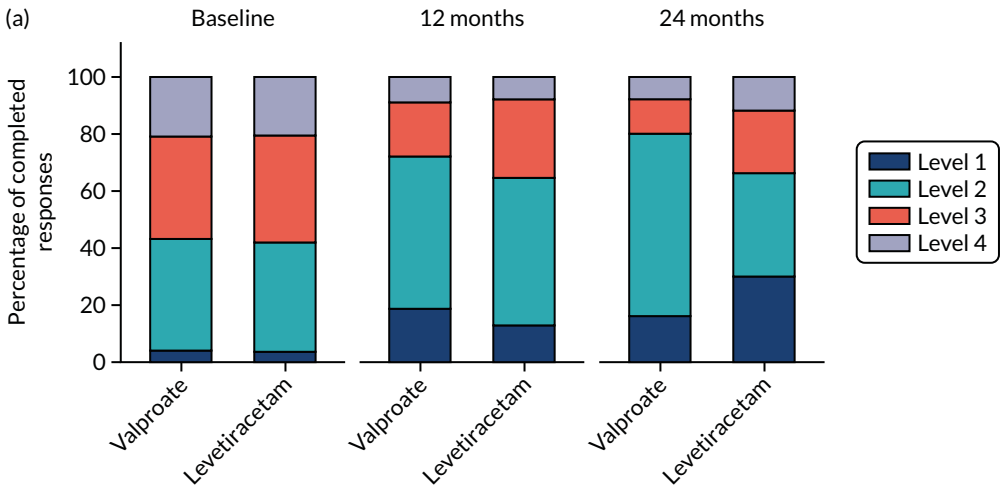


FIGURE 30 Distribution of participants' responses to each NEWQOL-6D attribute by treatment allocated and time: generalised and unclassified epilepsy. Levels range from 1 to 4, with 4 representing the most severe problem. The percentage of completed responses (%) are reported by intervention group. (a) Worry; (b) depression; (c) memory; (d) concentration; (e) control; and (f) stigma. (*continued*)

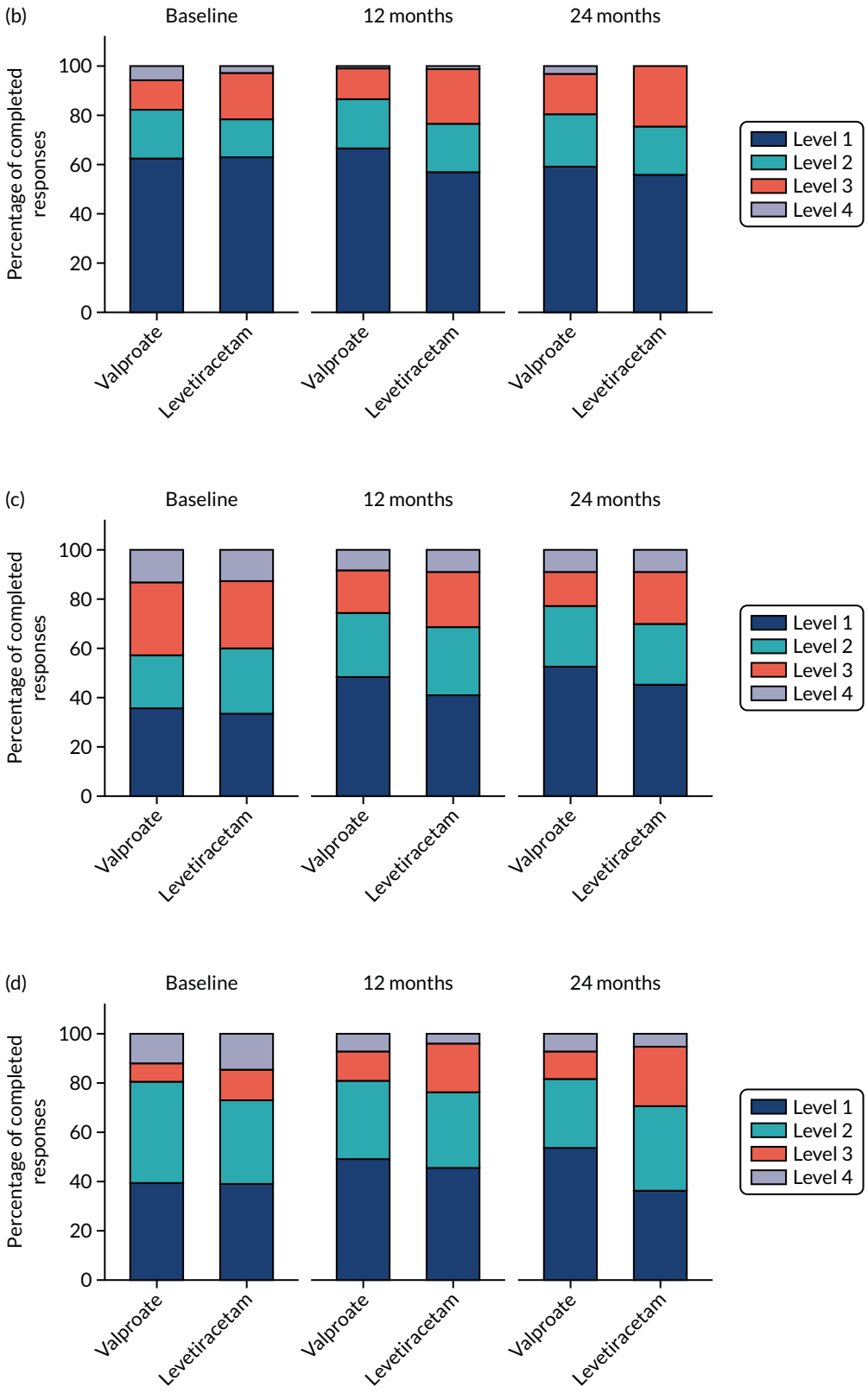


FIGURE 30 Distribution of participants' responses to each NEWQOL-6D attribute by treatment allocated and time: generalised and unclassified epilepsy. Levels range from 1 to 4, with 4 representing the most severe problem. The percentage of completed responses (%) are reported by intervention group. (a) Worry; (b) depression; (c) memory; (d) concentration; (e) control; and (f) stigma. (*continued*)

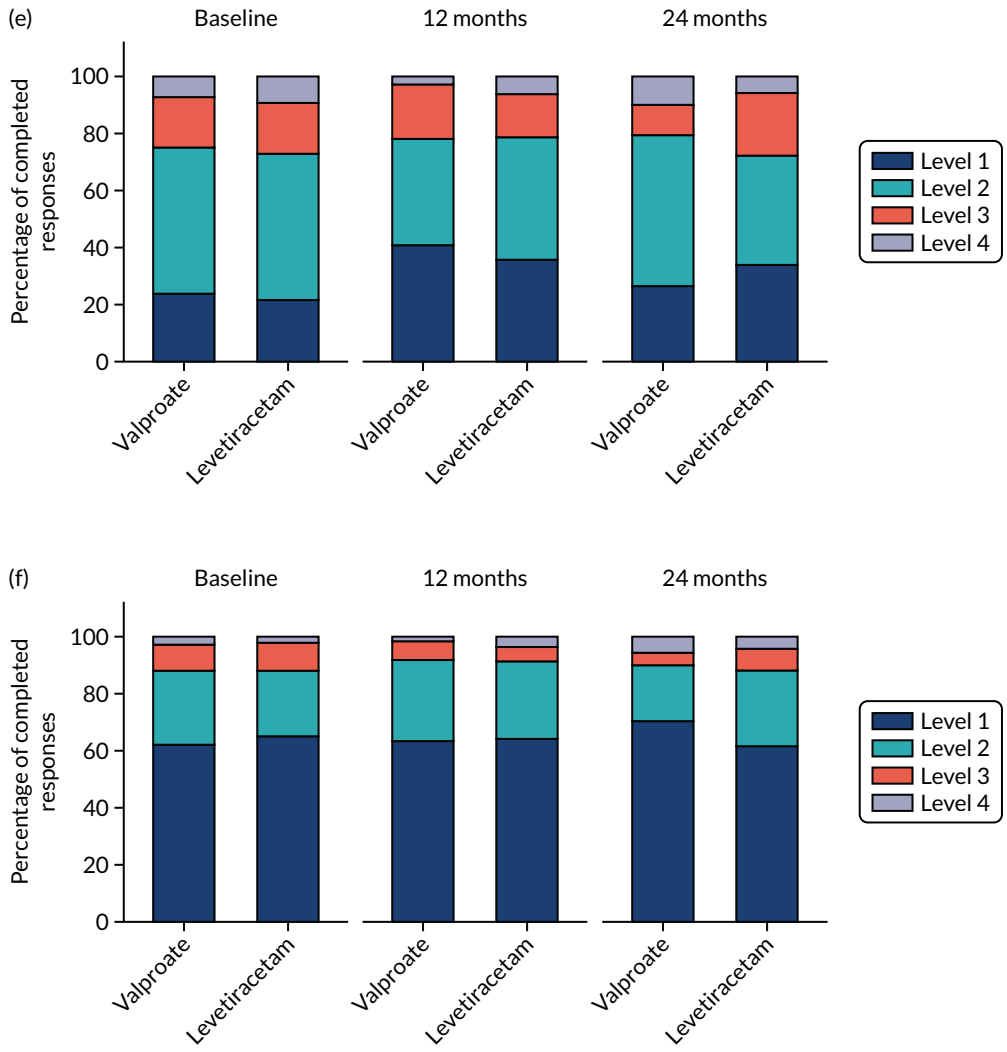


FIGURE 30 Distribution of participants' responses to each NEWQOL-6D attribute by treatment allocated and time: generalised and unclassified epilepsy. Levels range from 1 to 4, with 4 representing the most severe problem. The percentage of completed responses (%) are reported by intervention group. (a) Worry; (b) depression; (c) memory; (d) concentration; (e) control; and (f) stigma.

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