HEALTH TECHNOLOGY ASSESSMENT

VOLUME 22 ISSUE 23 MAY 2018
ISSN 1366-5278

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NHS
National Institute for Health Research

DOI 10.3310/hta22230

AntiEpileptic drug Monitoring in PREgnancy (EMPiRE): a double-blind randomised trial on effectiveness and acceptability of monitoring strategies

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Declared competing interests of authors: Manny Bagary reports personal fees from Eisai Co., Ltd, and personal fees from UCB Pharma outside the submitted work. Angela Pullen reports grants from GlaxoSmithKline plc., Cyberonics, Inc., Sanofi S.A., Desitin Pharma Ltd and UCB Pharma Ltd outside the submitted work. Sandra Eldridge is a member of the Health Technology Assessment Clinical Trials Board and National Institute for Health Research Clinical Trials Unit Support Funding.

Disclaimer: This report contains transcripts of interviews conducted in the course of the research and contains language that may offend some readers.

Published May 2018
DOI: 10.3310/hta22230

This report should be referenced as follows:

Thangaratinam S, Marlin N, Newton S, Weckesser A, Bagary M, Greenhill L, *et al*. AntiEpileptic drug Monitoring in PREgnancy (EMPiRE): a double-blind randomised trial on effectiveness and acceptability of monitoring strategies. *Health Technol Assess* 2018;**22**(23).

Health Technology Assessment is indexed and abstracted in *Index Medicus*/MEDLINE, *Excerpta Medica*/EMBASE, *Science Citation Index Expanded* (SciSearch®) and *Current Contents®*/ Clinical Medicine.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 4.236

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

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This report

The research reported in this issue of the journal was funded by the HTA programme as project number 09/55/38. The contractual start date was in September 2011. The draft report began editorial review in June 2016 and was accepted for publication in March 2017. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

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Abstract

AntiEpileptic drug Monitoring in PREgnancy (EMPiRE): a double-blind randomised trial on effectiveness and acceptability of monitoring strategies

Shakila Thangaratinam,[1,2,3]* Nadine Marlin,[3] Sian Newton,[1,3] Annalise Weckesser,[4] Manny Bagary,[5] Lynette Greenhill,[5] Rachel Rikunenko,[6] Maria D'Amico,[1,3] Ewelina Rogozińska,[1,2] Andrew Kelso,[7] Kelly Hard,[8] Jamie Coleman,[9] Ngawai Moss,[10] Tracy Roberts,[11] Lee Middleton,[12] Julie Dodds,[1,2,3] Angela Pullen,[13] Sandra Eldridge,[3] Alexander Pirie,[8] Elaine Denny,[4] Doug McCorry[5] and Khalid S Khan[1,2,3] on behalf of the EMPiRE Collaborative Network

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Background: Pregnant women with epilepsy on antiepileptic drugs (AEDs) may experience a reduction in serum AED levels. This has the potential to worsen seizure control.

Objective: To determine if, in pregnant women with epilepsy on AEDs, additional therapeutic drug monitoring reduces seizure deterioration compared with clinical features monitoring after a reduction in serum AED levels.

Design: A double-blind, randomised trial nested within a cohort study was conducted and a qualitative study of acceptability of the two strategies was undertaken. Stratified block randomisation with a 1 : 1 allocation method was carried out.

Setting: Fifty obstetric and epilepsy clinics in secondary and tertiary care units in the UK.

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Participants: Pregnant women with epilepsy on one or more of the following AEDs: lamotrigine, carbamazepine, phenytoin or levetiracetam. Women with a ≥ 25% decrease in serum AED level from baseline were randomised to therapeutic drug monitoring or clinical features monitoring strategies.

Interventions: In the therapeutic drug monitoring group, clinicians had access to clinical findings and monthly serum AED levels to guide AED dosage adjustment for seizure control. In the clinical features monitoring group, AED dosage adjustment was based only on clinical features.

Main outcome measures: Primary outcome – seizure deterioration, defined as time to first seizure and to all seizures after randomisation per woman until 6 weeks post partum. Secondary outcomes – pregnancy complications in mother and offspring, maternal quality of life, seizure rates in cohorts with stable serum AED level, AED dose exposure and adverse events related to AEDs.

Analysis: Analysis of time to first and to all seizures after randomisation was performed using a Cox proportional hazards model, and multivariate failure time analysis by the Andersen–Gill model. The effects were reported as hazard ratios (HRs) with 95% confidence intervals (CIs). Secondary outcomes were reported as mean differences (MDs) or odds ratios.

Results: A total of 130 women were randomised to the therapeutic drug monitoring group and 133 to the clinical features monitoring group; 294 women did not have a reduction in serum AED level. A total of 127 women in the therapeutic drug monitoring group and 130 women in the clinical features monitoring group (98% of complete data) were included in the primary analysis. There were no significant differences in the time to first seizure (HR 0.82, 95% CI 0.55 to 1.2) or timing of all seizures after randomisation (HR 1.3, 95% CI 0.7 to 2.5) between both trial groups. In comparison with the group with stable serum AED levels, there were no significant increases in seizures in the clinical features monitoring (odds ratio 0.93, 95% CI 0.56 to 1.5) or therapeutic drug monitoring group (odds ratio 0.93, 95% CI 0.56 to 1.5) associated with a reduction in serum AED levels. Maternal and neonatal outcomes were similar in both groups, except for higher cord blood levels of lamotrigine (MD 0.55 mg/l, 95% CI 0.11 to 1 mg/l) or levetiracetam (MD 7.8 mg/l, 95% CI 0.86 to 14.8 mg/l) in the therapeutic drug monitoring group than in the clinical features monitoring group. There were no differences between the groups on daily AED exposure or quality of life. An increase in exposure to lamotrigine, levetiracetam and carbamazepine significantly increased the cord blood levels of the AEDs, but not maternal or fetal complications. Women with epilepsy perceived the need for weighing up their increased vulnerability to seizures during pregnancy against the side effects of AEDs.

Limitations: Fewer women than the original target were recruited.

Conclusion: There is no evidence to suggest that regular monitoring of serum AED levels in pregnancy improves seizure control or affects maternal or fetal outcomes.

Future work recommendations: Further evaluation of the risks of seizure deterioration for various threshold levels of reduction in AEDs and the long-term neurodevelopment of infants born to mothers in both randomised groups is needed. An individualised prediction model will help to identify those women who need close monitoring in pregnancy.

Trial registration: Current Controlled Trials ISRCTN01253916.

Funding: This project was funded by the National Institute for Health Research (NIHR) Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 22, No. 23. See the NIHR Journals Library website for further project information.

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List of abbreviations

AED	antiepileptic drug
CI	confidence interval
DMC	Data Monitoring Committee
EMPiRE	AntiEpileptic drug Monitoring in PREgnancy
EQ-5D	EuroQol-5 Dimensions
HR	hazard ratio
IQR	interquartile range
LAEP	Liverpool Adverse Events Profile
MD	mean difference
NDDI-E	Neurological Disorders Depression Inventory for Epilepsy
QoL	quality of life
QOLIE-31	Quality Of Life In Epilepsy – 31-item questionnaire
RCT	randomised controlled trial
SD	standard deviation
TSC	Trial Steering Committee

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Plain English summary

Pregnant women with epilepsy who take medication for their seizures may have a decrease in the drug levels in their blood. This may worsen seizures. Some hospitals in the UK use regular blood tests to check the amount of drug in the mother's blood and offer to increase the dose of the medication if the levels reduce. Most hospitals in the UK do not monitor drug levels because existing National Institute for Health and Care Excellence and Scottish Intercollegiate Guidelines Network guidelines recommend a strategy based on monitoring clinical features. There is a lack of evidence to support either management.

The AntiEpileptic drug Monitoring in PREgnancy (EMPiRE) study aimed to find out if routine blood tests to monitor drug levels in pregnancy is better than management based on only clinical findings in preventing seizures and avoiding complications in pregnancy. We obtained women's views on the two strategies.

Of the 560 mothers with epilepsy on medication, the drug levels fell in 267 women. The risk of seizures and pregnancy complications as well as infants' birthweight and mothers' quality of life were similar in the group managed by monitoring drug levels regularly and in the group managed based on only clinical findings. We did not identify a link between an increase in seizures and a decrease in drug levels. Babies born to mothers whose drug levels were monitored regularly were exposed to a higher dose of the drug at birth. Women reported that the decisions that they make regarding epilepsy medication intake and dose are influenced by their feelings of responsibility for the health of their babies.

Our findings do not support regular blood monitoring of antiepileptic drug levels in pregnancy.

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Scientific summary

Background

Management of women with epilepsy on antiepileptic drugs (AEDs) is aimed at achieving seizure control on the lowest possible dose and number of AEDs. A reduction in serum AED levels in pregnancy is believed to be associated with seizure deterioration. A strategy of therapeutic drug monitoring of AED in pregnancy is considered to have the potential to minimise seizures.

Objectives

Primary

To determine, in pregnant women with epilepsy on AEDs who experience a 25% decrease in serum AED levels, if additional therapeutic drug monitoring reduces the risk of seizure deterioration in comparison to clinical features monitoring alone.

Secondary

- To determine if there is a relationship between the level of reduction in serum AED levels and seizures.
- To evaluate the effects of the two strategies on pregnancy complications.
- To determine the effect of two monitoring strategies on quality of life.
- To assess if there is a difference in the total AED exposure between the two randomised groups.
- To assess the adverse effects of AED in all women exposed to the drugs.
- To obtain women's views by a qualitative study.

Methods

Design

A double-blind, randomised trial nested within a cohort study was conducted and a qualitative study of acceptability of the two strategies was undertaken.

Setting

Fifty obstetric and/or epilepsy clinics in the UK between November 2011 and May 2015.

Participants

Inclusion criteria

- Pregnant women on AED with a viable pregnancy (< 24 weeks' gestation).
- Confirmed diagnosis of epilepsy.
- Women on AED monotherapy (lamotrigine, carbamazepine, phenytoin or carbamazepine) or polytherapy (lamotrigine with either carbamazepine, phenytoin or levetiracetam).
- Capable of understanding English.

Exclusion criteria

- Women aged < 16 years.
- A diagnosis of status epilepticus or non-epileptic seizures.

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- On non-lamotrigine polytherapy, sodium valproate monotherapy or polytherapy.
- Significant learning disability.
- Alcohol or substance abuse.
- Unable to complete seizure diaries or take AED in pregnancy.
- Participation in a blinded, placebo-controlled trial of an investigational medicinal product in pregnancy.

Outcome measures

Primary

Seizure deterioration defined as timing of all seizures after randomisation until 6 weeks after delivery.

Secondary

- Maternal: neurological, obstetric and quality of life.
- Fetal and neonatal: mortality and morbidity, birthweight, head circumference and cord blood serum AED levels.

Study conduct

Women with epilepsy on AED recruited in the study cohort were randomised to either therapeutic drug monitoring or clinical features monitoring if there was a $\geq 25\%$ decrease in serum AED levels at any time in pregnancy, compared with baseline or pre-pregnancy levels. Women and clinicians in the clinical features monitoring arm and non-randomised cohort were blinded to the serum AED levels. The seizure status was elicited from seizure diaries and complications from hospital records.

Sample size

We estimated that 660 randomised women are required to demonstrate a 25% seizure hazard decrease [hazard ratio (HR) $\approx$0.75] with therapeutic drug monitoring, providing 80% power (at a p-value of 0.05) and assuming an outcome-free survival rate of 60% in the clinical features monitoring group and 10% loss to follow-up.

Analysis

All analyses were on an intention-to-treat basis, and estimates of effect size (e.g. hazard or risk ratio) were presented as point estimates, with corresponding 95% confidence intervals (CIs). A multivariate failure time analysis of time to first seizure, and subsequent seizures, was performed using a generalisation of Cox proportional hazard model, taking into account the correlation of observations within each subject by incorporating robust standard errors for parameter estimates with the Andersen–Gill model.

Results

We recruited 560 mothers from 50 hospitals, randomised 267 women to either the therapeutic drug monitoring or clinical features monitoring group and included data from 257 women for primary analysis. There were no significant differences between the two groups for the time to first seizure (HR 0.82, 95% CI 0.55 to 1.2) or time to multiple seizures (HR 1.34, 95% CI 0.70 to 2.6). There were no differences between the arms in maternal and fetal complications, breastfeeding, birthweight, cord pH and quality of life. Cord blood levels of lamotrigine and levetiracetam were higher in the therapeutic drug monitoring group than in the clinical features monitoring group with adjusted mean differences (MDs) of 0.55 mg/l (95% CI 0.11 to 1.0 mg/l) and 7.8 mg/l (95% CI 0.86 to 14.8 mg/l), respectively, with similar levels of carbamazepine in both groups.

In comparison with the non-randomised group with stable serum AED levels, there were no significant increases in seizures in the clinical features monitoring (odds ratio 0.93, 95% CI 0.56 to 1.5) or therapeutic drug monitoring group (odds ratio 0.93, 95% CI 0.56 to 1.5). Increase in exposure to AED dose in women on monotherapy and polytherapy had no significant effect on maternal and neonatal outcomes, except for an increase in cord blood levels of lamotrigine (MD 0.55 mg/l, 95% CI 0.11 to 1.0 mg/l) and levetiracetam (MD 7.8 mg/l, 95% CI 0.86 to 14.8 mg/l) in the therapeutic drug monitoring group than in the clinical features monitoring group. There were no differences for cord blood levels of carbamazepine (MD –0.47 mg/l, 95% CI –1.5 to 0.6 mg/l) between the two groups.

Mothers with epilepsy on medication felt that they should weigh up their increased vulnerability to seizures during pregnancy against teratogenic effects of AEDs. We identified possible tension between health professionals' focus on drug adherence and the women's desire for their babies to be born without any health problems.

Conclusions

There is no evidence to support the theory that regular monitoring of AED drug levels in pregnancy offers additional benefit in seizure control than management based on only clinical features. Although there are no increases in short-term maternal or fetal complications with the drug monitoring strategy compared with a clinical-based strategy, the long-term neurodevelopment of babies exposed to higher serum AED levels in this group needs further evaluation.

Trial registration

This trial is registered as ISRCTN01253916.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

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Chapter 1 Introduction

Burden of the problem

Epilepsy complicates 0.6% of all pregnancies in the UK, affecting 0.5–1.0% of the general population.[1] Approximately one-third of people receiving antiepileptic drugs (AEDs) are of reproductive age,[2] and there has been a rise in the number of pregnancies exposed to AEDs in the past few decades.[3] Maternal mortality is 10-fold higher among pregnant women with epilepsy than among those without epilepsy.[1] In 2009–12, 14 maternal deaths in the UK were attributed to epilepsy[4] and sudden unexpected death in epilepsy, accounting for about 80% of deaths in women with epilepsy.[1,4] These were invariably a direct consequence of seizures. The numbers of maternal deaths related to epilepsy in the UK have been stagnant over the last 15 years. Confidential enquiries into maternal deaths have repeatedly highlighted concerns about epilepsy management during pregnancy.[4,5]

In addition to major risks to the mother, uncontrolled epilepsy with generalised tonic–clonic convulsions carries risk of harm to the fetus including miscarriage, fetal hypoxia and acidosis, and fetal loss.[6–8] The effect of epilepsy can impact daily living, resulting in loss of driving licence, negative impact on employment and relationships and reduced quality of life (QoL). Seizure control is central to the management of pregnant women with epilepsy, and mothers are often advised to continue the AED in pregnancy.

Antiepileptic drug exposure in utero is associated with congenital malformation,[9] with fetal risk related to the number of AEDs, AED type and, probably, AED dose.[10] Furthermore, the magnitude of AED dose exposure to the fetus in utero and the effect of continued AED intake in pregnancy on the long-term neurological development of children is not known. There is a consensus that the risks of uncontrolled convulsive seizures in the mother outweigh the potential teratogenic risk and any other adverse effect on offspring.[11,12]

Antiepileptic drug levels decrease in pregnancy in a proportion of women with epilepsy and are hypothesised to aggravate seizures.[13–15] Monitoring of serum AED levels in each trimester, and after delivery, has been recommended by the American Academy of Neurology based on consensus as a good practice.[16] In the UK, however, the National Institute for Health and Care Excellence and Scottish Intercollegiate Guidelines Network guidelines do not recommend regular AED monitoring in pregnancy because of a paucity of evidence.[12]

There are no randomised trials evaluating the effects of additional therapeutic drug monitoring (TDM) over clinical features monitoring (CFM) in determining the optimal management of women with epilepsy on AEDs in pregnancy. Furthermore, the acceptability of the two strategies, their impact on the QoL of the mother and pregnancy outcomes is not known.

Objectives

Primary objective

To determine, in pregnant women with epilepsy on AEDs who experience a 25% decrease from baseline in serum AED levels, if a strategy of additional therapeutic drug monitoring compared with clinical features monitoring alone to determine the optimal dose of AED reduces the risk of seizures.

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Secondary objectives

1. To determine if there is a relationship between the level of reduction in serum AED levels and seizures, by comparing women in a non-randomised cohort with stable levels with those in randomised cohorts with a decrease in levels.
2. To evaluate the effect of the two monitoring strategies on maternal and fetal outcomes in women with a decrease in serum AED levels.
3. To assess the effect of therapeutic drug monitoring versus clinical features monitoring on QoL in pregnant women with epilepsy on AEDs.
4. To identify any differences in total AED dose exposure between therapeutic drug monitoring and clinical features monitoring strategies.
5. To assess the adverse effects of AEDs in all women exposed to the drugs.
6. To gain insight into the way pregnant women with epilepsy rationalise and make sense of the management of AEDs in the context of their lives through a qualitative study.
7. To evaluate the cost-effectiveness of the two strategies.

Chapter 2 Methods

Study design

A double-blind, randomised trial nested within a cohort study was conducted and a qualitative study of acceptability of the two strategies was undertaken. The study received ethics approval from the National Research Ethics Service Committee West Midlands (reference number 11/WM/0164, trial registration 01253916).

Setting

The trial was conducted across 50 obstetric and/or epilepsy clinics in secondary and tertiary care units in the UK between November 2011 and May 2015.

Patient and public involvement

The Epilepsy Action charity assisted with the trial design and promotion. A member of the charity (APU) contributed in Trial Steering Committee (TSC) meetings to the general management of the project.

A patient representative (NMo) sat on the Trial Management Group and TSC panels and provided input towards the overall supervision of the trial.

Eligibility criteria

For inclusion in the trial, participants had to fulfil the following eligibility criteria.

Inclusion criteria

- Viable pregnancy of < 24 weeks' gestation.
- Confirmed diagnosis of epilepsy including primary, localised or unclassified.
- Lamotrigine monotherapy/polytherapy (with carbamazepine, phenytoin or levetiracetam) or carbamazepine monotherapy or phenytoin monotherapy or levetiracetam monotherapy.
- Capable of understanding the information provided.

Exclusion criteria

- Aged < 16 years.
- Documented status epilepticus in the last year or non-epileptic seizures in the last 2 years.
- Non-lamotrigine polytherapy or sodium valproate monotherapy or polytherapy.
- Participation in any blinded, placebo-controlled trials of investigational medicinal products in pregnancy.
- Significant learning disability.
- Unable to complete seizure diaries or recall frequency of seizures accurately.
- History of alcohol or substance abuse or dependence in the last 2 years.
- Expressed an intention not to take AEDs in pregnancy.

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Health technologies assessed

Women with a decrease in serum AED levels in pregnancy compared with baseline levels at booking or pre-pregnancy were randomised to management based on serum AED levels or to management based on clinical factors only.

Therapeutic drug monitoring group

The monthly levels of serum AED were communicated to the responsible clinicians. Clinicians managed women based on knowledge of serum AED levels in addition to clinical factors. The management involved discussion with the patient of potential risks of reduced serum levels, and the risks and benefits of an increase in AED dose to mother and baby. Women were provided treatment options including more frequent monitoring, increase in dosage of the AED immediately or delayed increase pending early testing.

Clinical features monitoring group

The clinician and mother were not informed of the serum AED levels, unless requested as part of an unblinding procedure. The decision to change the dose of AED was made by a responsible clinician based on clinical features alone.

Randomisation

Participants were allocated in 1 : 1 ratio to therapeutic drug monitoring or clinical features monitoring using a stratified block randomisation, with random block size of two, four or six to reduce predictability. Stratification variables were:

- baseline AED therapy: (1) lamotrigine monotherapy, (2) carbamazepine, phenytoin or levetiracetam monotherapy, or (3) lamotrigine polytherapy
- presence or absence of seizures 3 months prior to pregnancy.

Randomisation was carried out online using computer-generated randomisation sequences provided by the Nottingham Clinical Trials Unit.

Outcome

Primary outcome

The primary outcome was seizure deterioration, which was defined as time to first seizure, including first and subsequent seizures after randomisation, over the whole period of monitoring including 6 weeks post delivery.

Secondary outcomes

Maternal

- Neurological: the proportion of women experiencing seizures who were seizure free in the 3 months prior to consent, number of seizures per week and number of seizure-free days per week, mean daily AED dose exposure and adverse events as measured by the Liverpool Adverse Events Profile (LAEP).
- Obstetric: maternal death, mode of delivery, pre-term labour, induction of labour, pre-eclampsia, ante- and postpartum haemorrhage, admission to high-dependency/intensive care unit, breastfeeding, infection and gestational diabetes mellitus.
- QoL: epilepsy-specific QoL [as measured by the Quality Of Life In Epilepsy – 31-item questionnaire (QOLIE-31)] and a generic QoL [as measured by the EuroQol-5 Dimensions (EQ-5D)].

Fetal and neonatal

- Stillbirth, neonatal death, major congenital malformations (defined as structural abnormalities with surgical, medical or cosmetic importance diagnosed either antenatally or postnatally[17]), minor abnormalities, Apgar scores at 1 minute and 5 minutes, admission to neonatal unit, birthweight, head circumference, fetal growth and cord blood levels of AED.

Study conduct

Relevant neurological and obstetric histories were obtained from pregnant women with epilepsy at their booking/antenatal visit. Baseline data were collected on age, ethnicity, age at first seizure (excluding febrile seizures), seizure frequency over the previous 6 months, seizure types, epilepsy syndrome, aetiology of epilepsy, duration of epilepsy, current AED and dose, baseline serum AED level, indications of depression [as measured via the Neurological Disorders Depression Inventory for Epilepsy (NDDI-E)], learning difficulty, school leaving age, educational performance, current employment, previous AED pregnancy exposure, previous pregnancy complications, perinatal outcome, number of children, health of children and educational status of children at the first visit. Indications of depression at baseline were scored by participant responses to the NDDI-E. A score of > 15 out of 24 on the NDDI-E was considered to be indicative of depression and clinicians were requested to refer in accordance with local practice.

Participants were regularly monitored for serum AED levels from baseline at monthly intervals until 6–8 weeks post partum. Women were asked to record seizure activity in diaries specially developed for collecting trial data throughout the course of their participation. Women completed the EQ-5D (maximum score of 1), LAEP (maximum score of 76) and a Patient Costs Questionnaire at baseline, and all follow-up and postnatal visits. Responses to the QOLIE-31 (maximum score of 100 or QOLIE-31 overall health, maximum score of 10) were collected at baseline and in late pregnancy (i.e. 32–36 weeks' gestation). A higher score indicates a better health state.

Women with a $\geq$ 25% reduction in serum AED levels at any time in pregnancy, compared with baseline or pre-pregnancy levels, were randomised to therapeutic drug monitoring or clinical features monitoring. Women without a reduction in serum AED levels continued to be monitored in the non-randomised arm, and were randomised if their serum AED levels fell below 25% at any time until delivery. Women and clinicians in the clinical features monitoring arm and non-randomised cohort were blinded to the results. If randomised to the therapeutic drug monitoring arm, the serum levels were communicated to the participating centre within 1 working day of receipt of the test result from the laboratory. If appropriate, the clinician or the research midwife/nurse (on the advice of the clinician) contacted the participant to advise on a course of action within 7 working days of receipt of information from the trial unit. The current daily dose of AED and any adjustment was recorded. In exceptional circumstances, additional serum AED levels were requested from the central laboratory outside the trial visit plan, if deemed appropriate by the treating clinician (e.g. clinical suspicion of toxicity or non-adherence).

We obtained information on seizure status from the seizure diaries, and all maternal and fetal outcomes from clinical records. When women were admitted in labour, blood samples for serum AED levels were obtained alongside routine blood tests at any point from admission in labour up until discharge. After delivery, cord bloods were obtained for serum AED levels and cord pH. Details of the qualitative study are provided in *Chapter 4*, and details of amendments to study conduct and criteria are provided in *Appendix 1*.

The study has been reported in line with recommended guidelines.[18,19]

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Criteria for unblinding of serum levels in the control and non-randomised groups

The serum AED levels were revealed to the clinicians and women in the blinded groups (control and non-randomised) in the following circumstances:

- deterioration of seizures despite treatment – the serum AED level was revealed in these cases at the request of the clinician, similar to standard clinical practice
- clinical suspicion of toxicity
- if levels of AED were found to be above the therapeutic range with risks of toxicity
- results were requested by the clinician or patient for any other reason.

Withdrawal criteria

If a patient withdrew consent for the study, all data collected up to the point of withdrawal were retained unless the patient requested otherwise. If, for whatever reason, the patient discontinued monitoring, the participant was not withdrawn from the study and data collection continued to allow intention-to-treat analysis, unless consent to do this was withdrawn. Rates were monitored to detect differential dropout, which can bias clinical trial results and reduce the power of the study.

Sample size estimation

A large, prospective registry of pregnant women with epilepsy suggested that around 40% of women experience seizures during pregnancy.[20] We set the outcome-free survival rate under clinical features monitoring at 60% and estimated sample sizes for various effect sizes smaller than what was observed in our systematic review. *Table 1* gives a range of estimates of sample sizes for different powers and effect sizes for the primary outcome of time to first seizure.

We aimed to collect data from at least 594 randomised women, giving 80% power (at $p = 0.05$) to detect a 25% seizure hazard decrease [hazard ratio (HR) ≈0.75]. We considered 25% to be the minimally important difference in seizure deterioration to be achieved, given the potential drawbacks of increasing AED dose exposure. We assumed a loss to follow-up of 10%, and estimated the need to randomise 660 women with a reduction in serum AED level.

TABLE 1 Sample size estimates for different powers and effect sizes

	Total sample size	
Control survival rate (60%)	80% power	90% power
Increased to 78% (hazard ratio ≈0.60)	182	244
Increased to 76% (hazard ratio ≈0.65)	258	344
Increased to 73% (hazard ratio ≈0.70)	380	508
Increased to 71% (hazard ratio ≈0.75)	594	794

Analysis

Participants were analysed belonging to the group to which they were randomised, unless they were randomised in error. All estimates of effect size (e.g. hazard or risk ratio) were presented as point estimates, with corresponding 95% confidence intervals (CIs) and *p*-values. All analyses were carried out using Stata® version 12.0 (StataCorp LP, College Station, TX, USA).

The primary analysis of time to first seizure was performed using a Cox proportional hazards model. The primary multivariate failure time analysis of time to first seizure was performed using a generalisation of the Cox proportional hazards model, taking into account the correlation of observations within each subject by incorporating robust standard errors for parameter estimates, the Andersen–Gill model.[21] For both models, survival analysis was performed on a daily scale. Multiple seizures of the same or different types on the same day were not considered separately. An event was defined as at least one seizure of any type on a calendar day. Censoring occurred at the first date with missing information on seizure occurrence, or at end of follow-up if no event was recorded and follow-up was complete without missing records.

In addition to the treatment allocation, all primary and secondary models included the randomisation factors of AED type (lamotrigine monotherapy/carbamazepine, phenytoin or levetiracetam monotherapy/lamotrigine polytherapy) and seizures 3 months prior to consent (yes/no) as covariates in the model. To increase the precision of the treatment effect estimate, we also adjusted for the following baseline values that were determined a priori: maternal age, age at first seizure (excluding febrile seizures) and general seizure classification at baseline (tonic–clonic seizure/non-tonic–clonic seizure/unclassified).

Secondary analyses of differences between the two randomised arms for pregnancy outcomes, cord blood serum AED levels and QoL were performed using analysis of covariance. We used Poisson models for analyses of the LAEP, logistic models for binary outcomes, ordered logistic regression for the categorical outcome 'breastfeeding' and linear regression for continuous outcomes.

We analysed the association between the reduction in serum AED levels and seizure status using logistic regression models for the binary outcome of seizure-free status by the end of follow-up, and Poisson regression models for weekly seizure rate and number of seizure days per week. Seizure-free status was analysed including randomised and non-randomised participants. Rates were compared between clinical features monitoring and the non-randomised cohort. AED dose exposure was compared between therapeutic drug monitoring, clinical features monitoring and the non-randomised cohort using linear regression. For analysis of participants on multiple AEDs, we used multivariate multiple regression to analyse the two drugs together.

Fetal outcomes were analysed using mixed models to account for clustering of twins by mother (2.7% of pregnancies in study population). Convergence issues were dealt with by using a simpler analysis of covariance model ignoring clustering. We compared these results against a model including only one twin per pair, and in all cases the model results were very similar. The number of twins included in any analysis was very small and the impact of ignoring the clustering in these situations was deemed sufficiently low.

Assumption checks and sensitivity analysis

Extreme values were checked as part of the data cleaning procedure. Any remaining outliers were considered to be true data values and therefore analysed as reported. However, using box plots we identified one participant with extremely large numbers of seizures. We assessed the robustness of the secondary analysis of seizure rates by excluding this value and interpreted the results accordingly. For survival models, the proportional hazards assumption was checked using Schoenfeld residuals, log–log plots and through inclusion of time-dependent effects; subgroup effects were presented to investigate violations and compared using the Wald test for treatment–covariate interactions. We investigated whether or not any treatment effect differed by seizure type by only considering tonic–clonic seizures as outcomes.

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Missing values

Withdrawals and those lost to follow-up were included in the analysis up to the last point that data are available. If the number of seizures was unknown for a date or a date range, we contacted the mothers by telephone or in person to obtain missing details. When this was not possible, records were reviewed by two independent neurologists (DM and AK), who commented on the likelihood of seizure and type of seizure in the missing slot. When the neurologists were not able to provide this opinion, or there was a discrepancy in their opinion, the opinion of a third neurologist (Shanika Samarasekera) was sought. When all neurologists were unable to provide estimation on likelihood of seizure, the average seizure rate for tonic–clonic seizures and the rate for non-tonic–clonic seizures over the period of the participant's completed diary were applied.

When the seizure type was missing or no other data for the seizure type were available, the average rate over any seizure type was used. If multiple seizures occurred during a time frame, they were equally spaced out over the time frame. If the number of seizures was larger than the number of days, the seizures were equally spaced out over each day in the time frame. A sensitivity analysis was conducted for the analysis of time to first seizure to investigate if an interval censoring approach showed a different result. When there were missing data on seizure occurrence, participants were censored at the first date on which seizure occurrence was known. A sensitivity analysis will be performed for the analysis of multiple events ignoring any dates or date ranges in which seizure occurrence is unknown.

Sensitivity analysis for interval analysis for time to first seizure

This sensitivity analysis was planned a priori but not conducted. The reasons are as follows.

The exact date of the first seizure was uncertain in eight women. Three women had substantially more seizures than the number of days in the period of uncertainty. For these women we assumed daily seizures, as the actual number of seizures occurring on a single day is irrelevant for the primary analysis.

Three women reported more than one seizure occurring during a period of 3–6 weeks. Interval censoring approaches standardly available in the statistical packages allow only one event to occur during the period of uncertainty. Allowing for multiple events during the period of uncertainty would require the application of multistate models, which would probably introduce other issues, such as convergence problems. Two women had a single seizure during 1 month. Here, the interval censoring approach standardly available could have been applied. However, as a result of the small number and the issues arising for other women (as described in the previous paragraph), it was decided not to perform this analysis.

Oversight of the trial

The management of our study included an element of expert advice that was entirely independent from the investigators and their host institution(s). The trial was overseen by a 15-member TSC, which included three independent members and a consumer representative from Epilepsy Action. There were three independent members in the five-member Data Monitoring Committee (DMC). The terms of reference and charter for the DMC were determined at the outset, taking into account issues relevant to the monitoring of this study.[22]

Health economics analysis

The original sample size for the study was 660 randomised women. In 2014, given the slow rate of recruitment of the trial, the funder, after discussion with the DMC and TSC, decided not to extend the recruitment period of the trial, prior to achievement of the planned sample size. The economic analysis was integral to the initial study design, but given that the planned sample size was not recruited, it was postponed pending results to see if it was justified. Given that the study ultimately found no evidence to support that regular monitoring of AED drug levels in pregnancy offers additional benefit in seizure control than management based only on clinical features, any justification for an economic evaluation has not materialised.

Chapter 3 Results

Flow of women recruited in the study

We recruited 593 women: 580 for the cohort and 13 for the qualitative study. The median number of women recruited per centre was nine [interquartile range (IQR) 6–13]. Of the 580 women recruited into the cohort, 20 were recruited but subsequently found to fail the inclusion criteria, resulting in 560 women who were monitored for a reduction in serum AED levels. Less than 1% of participants ($n = 6$) were recruited twice into the study because they became pregnant again during the trial period. Overall, 263 women had a reduction in serum AED level at some point in their pregnancy and were randomised to therapeutic drug monitoring ($n = 130$) or clinical features monitoring ($n = 133$) groups, and the remaining 293 had stable serum AED levels until delivery. Four women who were randomised in error after the end of pregnancy were analysed with the non-randomised group. Complete outcome data for the primary analysis were available from 127 women (98%) in the therapeutic drug monitoring group, 130 (98%) in the clinical features monitoring group and 294 (99%) in the non-randomised group (*Figure 1*).

Characteristics of women included

A total of 85% of recruited women in the therapeutic drug monitoring, clinical features monitoring and non-randomised groups were white. Around 60% in each of the groups had been educated to Advanced level (A level) or higher. Half of all women in the non-randomised cohort (50%) were nulliparous, and the corresponding figures were 58% and 54% in therapeutic drug monitoring and clinical features monitoring groups, respectively. The rates of congenital abnormalities in previous pregnancies were between 5% and 8% of women in the therapeutic drug monitoring, clinical features monitoring and non-randomised groups. There was a history of mental illness in about one-tenth of the women (*Table 2*).

Tonic–clonic seizure was the most common type of seizure, being diagnosed in 80% (100/130) of women in the therapeutic drug monitoring group, 82% (109/133) in the clinical features monitoring group and 81% (237/294) in the non-randomised cohort. One-quarter of women in each of the randomised groups (therapeutic drug monitoring: 26%, 34/130; clinical features monitoring: 24%, 32/133) and one-third in the non-randomised group (29%, 84/294) were seizure free for 3 months before pregnancy. Lamotrigine monotherapy was the most common AED medication taken by around half of the women at baseline. Lamotrigine polytherapy was taken by one-tenth in the therapeutic drug monitoring (11%, 14/130) and clinical features monitoring (9%, 12/133) groups, and by 5% in the non-randomised cohort (15/294). The doses of individual AEDs taken at the time of randomisation in the therapeutic drug monitoring and clinical features monitoring groups are provided in *Table 3*.

Baseline QoL measurements are provided in *Table 4*. Scores for the NDDI-E, QoL (EQ-5D), LAEP and QOLIE-31 were balanced across the therapeutic drug monitoring and clinical features monitoring groups.

Time to randomisation from consent

Figure 2 shows the time from baseline to randomisation for randomised participants. Randomisation was performed, on average, 68 days [standard deviation (SD) 43 days] from baseline (median 59 days, IQR 40–96 days).

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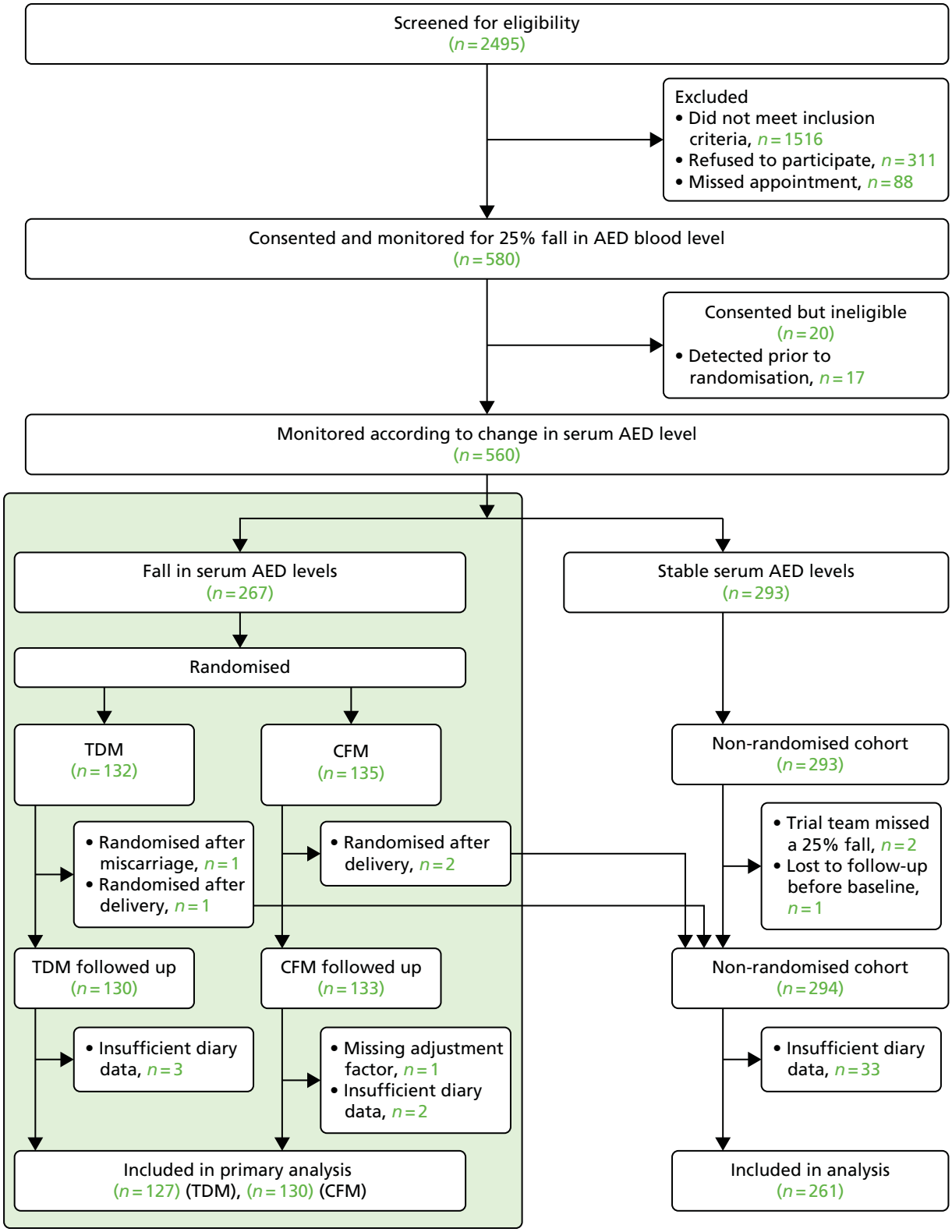

FIGURE 1 Consolidated Standards of Reporting Trials flow chart. CFM, clinical features monitoring; TDM, therapeutic drug monitoring.

TABLE 2 Baseline demographic and obstetric details of women included in the study

Variable	Trial group, *n* (%)		
	Randomised		Non-randomised (*N* = 294)
	TDM (*N* = 130)	CFM (*N* = 133)	
Ethnic group	*n* = 130	*n* = 133	*n* = 294
White	113 (87)	118 (89)	253 (86)
Black	2 (2)	3 (2)	6 (2)
Asian	13 (10)	7 (5)	25 (9)
Mixed	0 (0)	2 (2)	8 (3)
Other	2 (2)	3 (2)	2 (1)
Highest qualification	*n* = 127	*n* = 133	*n* = 292
Degree level	50 (39)	49 (37)	114 (39)
A level	29 (23)	33 (25)	68 (23)
GCSE	44 (35)	48 (36)	87 (30)
Below GCSE	4 (3)	3 (2)	23 (8)
Smoking status	*n* = 130	*n* = 133	*n* = 294
Smoker	17 (13)	14 (11)	34 (12)
Ex-smoker	30 (23)	31 (23)	90 (31)
Non-smoker	83 (64)	88 (66)	170 (58)
Alcohol units per week	*n* = 130	*n* = 133	*n* = 294
0	122 (94)	117 (88)	266 (91)
1–9	8 (6)	16 (12)	25 (9)
≥ 10	0 (0)	0 (0)	3 (1)
Parity	*n* = 130	*n* = 133	*n* = 294
0	75 (58)	72 (54)	147 (50)
1–4	55 (42)	59 (44)	144 (49)
≥ 5	0 (0)	2 (2)	3 (1)
Previous children	*n* = 76	*n* = 100	*n* = 225
Neonatal deaths	1 (1)	1 (1)	2 (1)
Stillbirths	0 (0)	0 (0)	3 (1)[a]
At least one congenital abnormality in previous children	7 (7)	4 (5)	17 (8)
Medical history	**n = *130***	**n = *133***	**n = *293***
Maternal congenital abnormalities	5 (4)	5 (4)	5 (2)
Diabetes	3 (2)	1 (1)	9 (3)
Chronic hypertension	2 (2)	2 (2)	7 (2)
Renal disease	3 (2)	2 (2)	5 (2)
HIV infection	0 (0)	0 (0)	1 (0)
Learning difficulties	3 (2)[b]	1 (1)	11 (4)[c]
Mental illness	19 (15)	15 (11)	33 (11)

A level, Advanced level; CFM, clinical features monitoring; GCSE, General Certificate of Secondary Education; HIV, human immunodeficiency virus; TDM, therapeutic drug monitoring.

a There were 226 participants analysed in this group.

b There were 129 participants analysed in this group.

c There were 292 participants analysed in this group.

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TABLE 3 Baseline neurological characteristics of women in the study

Variable	Trial group		
	Randomised		Non-randomised cohort
	TDM	CFM	
Age at first seizure (years), mean (SD) [*n*]	16.8 (8) [130]	17.0 (7) [132]	16.1 (7) [290]
Years since first seizure, mean (SD) [*n*]	12.2 (8) [121]	12.1 (7) [124]	16.1 (8) [261]
Seizures 3 months prior to pregnancy [*N*]	34.0 (26) [130]	32.0 (24) [133]	84.0 (29) [294]
Seizure classification,[a] *n* (%)	*N* = 130	*N* = 133	*N* = 294
TCS	100 (80)	109 (82)	237 (81)
Absence	29 (22)	35 (26)	85 (29)
Myoclonus	13 (10)	20 (15)	33 (11)
Simple	19 (15)	20 (15)	30 (10)
Complex	36 (28)	19 (14)	57 (19)
Unclassified/other	6 (5)	7 (5)	14 (5)
AED intake at baseline, *n* (%)	*N* = 130	*N* = 133	*N* = 294
LTG monotherapy	68 (52)	70 (53)	148 (50)
CBZ, PHT or LEV monotherapy	48 (37)	51 (38)	131 (45)
LTG polytherapy	14 (11)	12 (9)	15 (5)
Type of AED intake at baseline, *n* (%)	*N* = 130	*N* = 133	*N* = 294
CBZ	16 (12)	20 (15)	54 (18)
LTG	68 (52)	70 (53)	148 (50)
LEV	31 (24)	31 (23)	77 (26)
PHT	1 (1)	0 (0)	0 (0)
LTG and LEV	14 (11)	11 (8)	15 (5)
LTG and CBZ	0 (0)	1 (1)	0 (0)
Dose of AED at randomisation (mg), mean (SD) [*n*]			
CBZ only	581.3 (339.1) [16]	695.0 (336.4) [20]	
LTG only	246.3 (124.4) [68]	242.9 (148.5) [70]	
LEV only	1500.0 (724.6) [31]	1572.6 (880.8) [31]	
PHT only	[0]	200.0 [1]	
LTG and LEV, LTG dose	448.2 (215.8) [14]	379.6 (92.8) [11]	
LTG and LEV, LEV dose	1767.9 (846.2) [14]	2100.0 (1119.3) [10]	
LTG and CBZ, LTG dose	[0]	200.0 [1]	
LTG and CBZ, CBZ dose	[0]	300.0 [1]	

CBZ, carbamazepine; CFM, clinical features monitoring; LEV, levetiracetam; LTG, lamotrigine; PHT, phenytoin; SD, standard deviation; TCS, tonic–clonic seizure; TDM, therapeutic drug monitoring.
a Some women experience more than one seizure type.

TABLE 4 Baseline scores for questionnaires

Variable	Trial group, mean (SD) [*n*]		
	Randomised		
	TDM (*N* = 130)	CFM (*N* = 133)	Non-randomised (*N* = 294)
NDDI-E[a]	9.7 (3.3) [130]	9.9 (3.6) [133]	10.1 (3.5) [284]
EQ-5D[b]	0.90 (0.17) [126]	0.90 (0.16) [127]	0.89 (0.18) [267]
LAEP[c]	34.3 (8.9) [124]	34.9 (10.4) [121]	35.3 (9.2) [259]
QOLIE-31 score[d] (UK)	73.7 (14.6) [128]	72.8 (15.5) [128]	71.0 (16.8) [274]
QOLIE-31 overall health[e] (UK)	7.0 (1.8) [127]	7.0 (1.9) [128]	7.1 (1.8) [273]

CFM, clinical features monitoring; SD, standard deviation; TDM, therapeutic drug monitoring.
a Maximum score of 24.
b Maximum score of 1.
c Maximum score of 76.
d Maximum score of 100.
e Maximum score of 10.

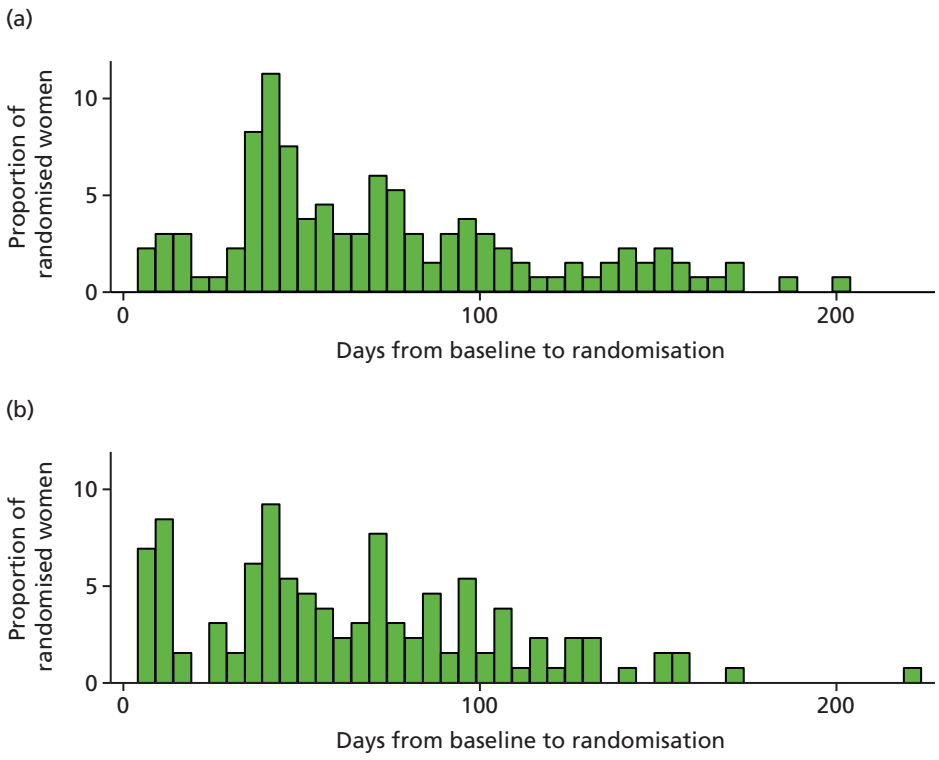

FIGURE 2 Time from baseline to randomisation in days. (a) Clinical features monitoring; and (b) therapeutic drug monitoring.

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Effects of therapeutic drug monitoring and clinical features monitoring strategies for antiepileptic drug dosing on maternal seizures

A total of 257 women provided a cumulative analysis time of 35,859 days from randomisation to censoring, with 25,001 days from randomisation to first seizure. The median time of follow-up from randomisation to censoring was 153 (IQR 115–179) and 134 (IQR 84–169) days for the therapeutic drug monitoring and clinical features monitoring groups, respectively. The number of days with seizure and actual number of seizures that occurred in both groups are provided in *Table 5*.

Seizure data were captured from randomisation to the first day of missing data. One-quarter of women in the clinical features monitoring group had a total observation period of < 12 weeks in comparison to 8% of the therapeutic drug monitoring group. A total observation period of 12–24 weeks was seen in half of each randomised group, and one-quarter of the clinical features monitoring and one-third of the therapeutic drug monitoring participants had a total observation period of 24–36 weeks. One woman in each group had seizure data captured for > 36 weeks. The mean number of days with captured seizure data was higher for the therapeutic drug monitoring group by 19 days.

TABLE 5 Seizure data from randomisation to censoring (as defined by the first date of missing diary data)

	Randomised group, *n* (%)	
Variable	TDM (*N* = 127)	CFM (*N* = 130)
Total observation period (weeks)		
< 12	11 (8)	32 (25)
12 to < 24	69 (54)	65 (50)
24 to < 36	46 (36)	32 (25)
≥ 36	1 (1)	1 (1)
Median (IQR) (days)	153 (115–179)	134 (84–169)
Number of days with any seizures		
0	79 (66)	80 (63)
1–29	36 (30)	43 (34)
30–59	5 (4)	2 (2)
60–89	0 (0)	2 (2)
≥ 90	7 (6)	3 (2)
Median (IQR)	0 (0–3)	0 (0–4)
Total number of seizures		
0	79 (64)	80 (62)
1–9	29 (24)	26 (20)
10–99	10 (8)	20 (16)
100–499	6 (5)	3 (2)
≥ 500	3 (2)	1 (1)
Median (IQR)	0 (0–4)	0 (0–5)

CFM, clinical features monitoring; TDM, therapeutic drug monitoring.

Two-thirds of each randomised group did not experience any seizures after randomisation, whereas approximately one-third of both groups experienced 1–29 days with seizures. Number of days with seizures was similar in both groups (*Figure 3*). Less than one-quarter of women in both groups had up to nine seizures post randomisation. The proportion of women who experienced 10–99 seizures was twice as high in the clinical features monitoring group (16%) as in the therapeutic drug monitoring group (8%). Small numbers of women in each group experienced > 100 seizures after randomisation and ≥ 30 days of seizures.

There were no differences in the proportion of women who experienced at least one seizure in the therapeutic drug monitoring (48/127, 38%) and clinical features monitoring (50/130, 38%) groups, with a mean observed time to first seizure of 28 days (SD 42 days) in the therapeutic drug monitoring group and 27 days (SD 36 days) in clinical features monitoring group. There was a 20% reduction in the time to first seizure with therapeutic drug monitoring compared with clinical features monitoring, a difference that was not significant (HR 0.8, 95% CI 0.55 to 1.2). The CI suggests a possible effect of between a 45% decrease and a 20% increase in seizure rate with therapeutic drug monitoring and includes a HR of 0.75; therefore, the possibility of a clinically relevant difference between therapeutic drug monitoring and clinical features monitoring cannot be rejected. *Figure 4* shows the results of the Cox regression of time to first seizure and the corresponding Kaplan–Meier curve. Assumption checks indicated no violation of the proportional hazards assumption globally ($p = 0.17$). However, some violation was detected for adjustment factor maternal age ($p = 0.003$), indicating that the influence of age on seizure occurrence changes over time. After including a time-dependent effect for age, the proportional hazards assumption was satisfied for all covariates. Including the time-dependent effect resulted in a minor change to the CI, but not the effect size or statistical significance (HR 0.8, 95% CI 0.54 to 1.3). These investigations supported the use of the Cox model for our analysis.

Maternal age at baseline slightly increased with date of randomisation over the 3-year study period ($p = 0.11$), which may explain some of the time-dependent effect. The effect of age as a risk factor may also have varied over time, indicating that higher maternal age at baseline might have carried a larger risk later in the study period than at the start of the study period.

Ninety-eight (38%) women experienced only one seizure, 75 (29%) experienced two or more seizures and 72 (28%) experienced three or more seizures. Of the 98 women who had suffered a first seizure, 75 women experienced a second seizure, 35 in the therapeutic drug monitoring group and 40 in the clinical features monitoring group, with a mean duration to second seizure of 12.1 and 11.6 days, respectively. Subsequently, 72 women with a second seizure had a third seizure, 33 in the therapeutic

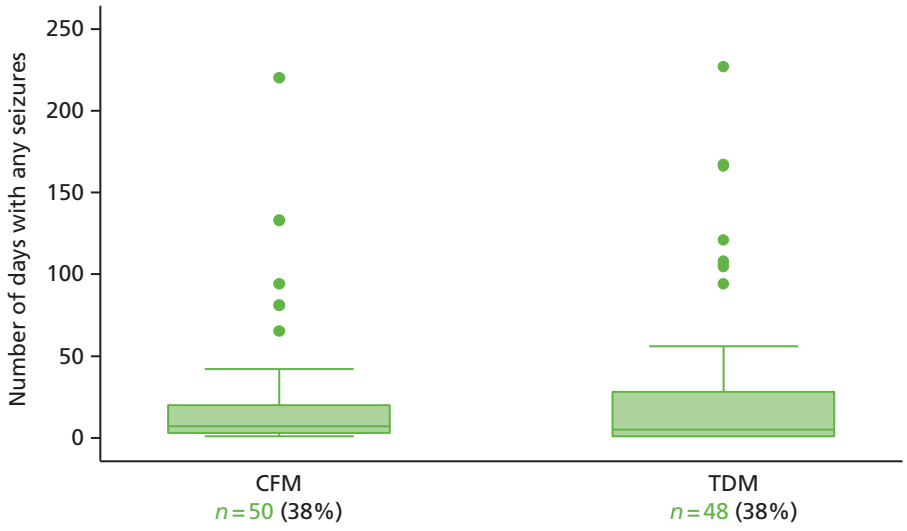

FIGURE 3 Seizure diaries: total number of days with any seizures from randomisation to the end of follow-up by allocation group, excluding women with no seizures. CFM, clinical features monitoring; TDM, therapeutic drug monitoring.

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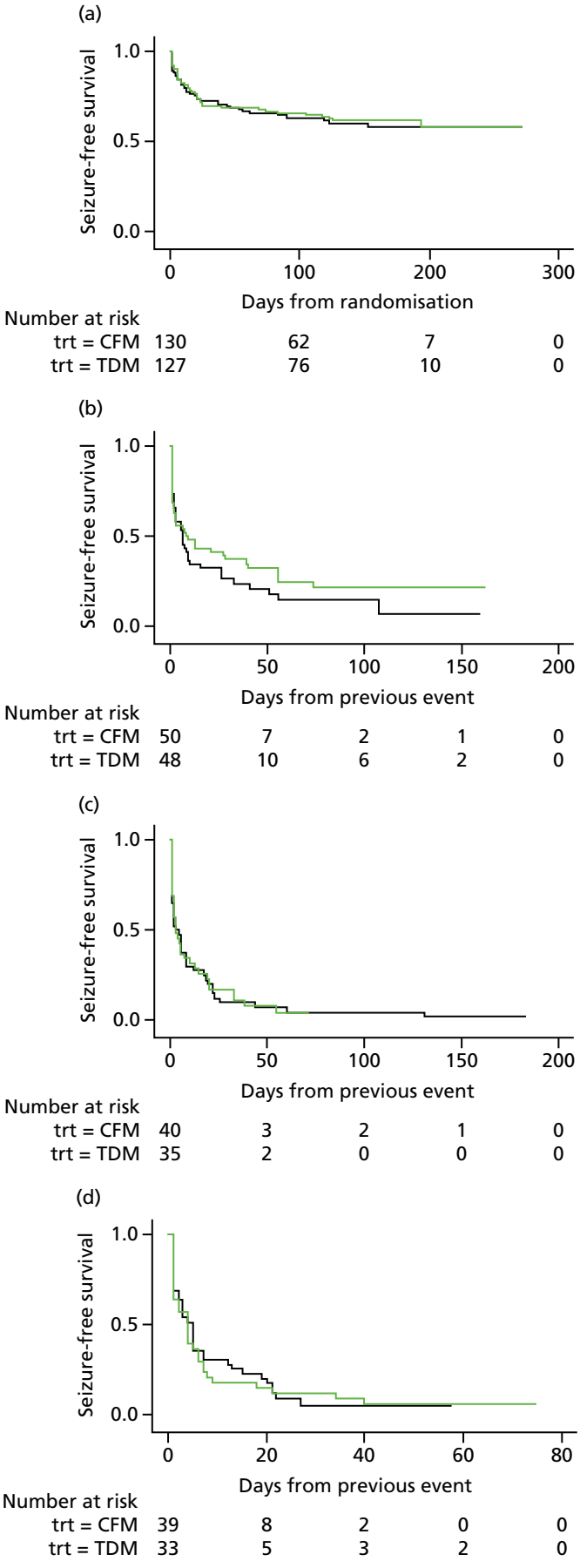

FIGURE 4 Survival graphs for time to first seizure and subsequent seizures. (a) Event 1; (b) event 2; (c) event 3; and (d) event 4. CFM, clinical features monitoring; TDM, therapeutic drug monitoring; trt, treatment allocation.

drug monitoring group (median 3 days, IQR 1–17 days) and 39 in the clinical features monitoring group (median 3 days, IQR 1–13 days).

The analysis of overall time to first seizure and subsequent seizures showed a larger increase with therapeutic drug monitoring than clinical features monitoring, but this was not significant (HR 1.3, 95% CI 0.7 to 2.6). *Figure 5* shows the Kaplan–Meier curve of the multiple failure time analysis of time to first seizure and subsequent seizures.

Assumption checks indicated violations of the proportional hazards assumption globally and for all covariates. To investigate the source of the violations we performed the Cox regression model including time-dependent effects for all covariates. Only maternal age showed a significant time-dependent effect, which was subsequently included in the Cox regression. The resulting model showed no indication of proportional hazards assumption violation for any covariates. Including the time-dependent effect resulted in a minor change to the effect size and CI, with no changes to statistical significance (HR 1.4, 95% CI 0.73 to 2.6).

Additionally, we investigated treat–covariate interactions by estimating effects within subgroups of each covariate. The subgroup effect sizes were mostly similar and are shown in *Table 6*. No statistically significant effect modification was detected for any covariate.

These investigations supported the use of the Cox model for our analysis.

Proportional hazards assumption checks

For time to first seizure, and time to multiple seizures, we did not find any differences between the subgroups based on seizure status 3 months before pregnancy, type of AED intake at baseline and the type of seizure (see *Table 6*).

Sensitivity analysis

We undertook a sensitivity analysis by including only women with tonic–clonic seizures. For the analysis of time to first tonic–clonic seizure, 257 women provided a total analysis time of 31,572 days from randomisation to first seizure or censoring. *Table 7* shows that the risk of time to first seizure was lower in the therapeutic drug monitoring group than in the clinical features monitoring group, but this difference was not statistically significant (HR 0.80, 95% CI 0.43 to 1.5). *Figure 6* shows the results of the Cox regression of time to first tonic–clonic seizure and the corresponding Kaplan-Meier curve.

Figure 7 shows the Kaplan–Meier curve of the multiple failure time analysis of time to first tonic–clonic seizure and subsequent seizures.

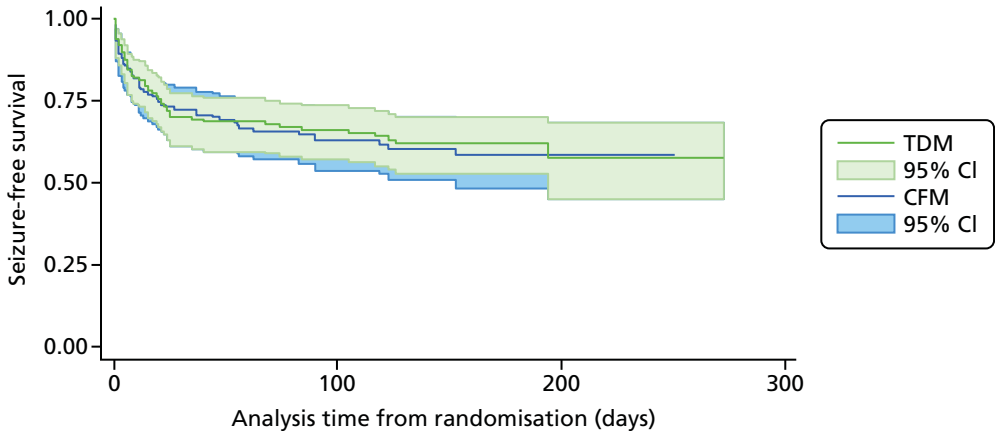

FIGURE 5 Survival graphs for time to first seizure and time to subsequent seizures after randomisation. Time to (a) event 1; (b) event 2; (c) event 3; and (d) event 4. CFM, clinical features monitoring; TDM, therapeutic drug monitoring; trt, treatment allocation.

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TABLE 6 Assumption check: primary analysis within subgroups of covariates

Covariate	Subgroup	*n*	Subgroup TDM effect, HR (95% CI)
Seizures 3 months prior to pregnancy	No	192	1.0 (0.35 to 2.8)
	Yes	65	1.4 (0.68 to 2.8)
Baseline AED group	LTG monotherapy	133	1.1 (0.41 to 3.0)
	CBZ, PHT or LEV monotherapy	99	1.5 (0.56 to 4.1)
	LTG polytherapy	25	1.3 (0.27 to 6.3)
Maternal age (years)[a]	< 25	50	1.0 (0.35 to 2.9)
	25 to < 35	166	1.8 (0.68 to 4.6)
	≥ 35	41	1.1 (0.21 to 5.5)
Age at first seizure (years)[a]	< 10	37	0.28 (0.07 to 1.1)
	10 to < 20	138	1.9 (0.90 to 4.2)
	≥ 20	82	3.3 (0.91 to 12.1)
Baseline broad seizure classification	TCS	96	0.40 (0.11 to 1.4)
	Non-TCS	154	1.4 (0.71 to 2.8)
	Unspecified only	7	0.7 (NA)

CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; NA, not available; PHT, phenytoin; TCS, tonic–clonic seizure; TDM, therapeutic drug monitoring.
a Maternal age and age at first seizure were grouped into clinically meaningful categories for presenting subgroup effects. However, tests for interaction were performed on the continuous covariate.

TABLE 7 Sensitivity analysis: first event for tonic–clonic seizure only

		Analysis time (days), mean (SD)		Proportion of women with any seizures		
Model	*n*	TDM	CFM	TDM	CFM	TDM effect, HR (95% CI)
Time to first TCS	257	132 (63)	114 (65)	0.16	0.17	0.80 (0.43 to 1.50)

CFM, clinical features monitoring; TCS, tonic–clonic seizure; TDM, therapeutic drug monitoring.

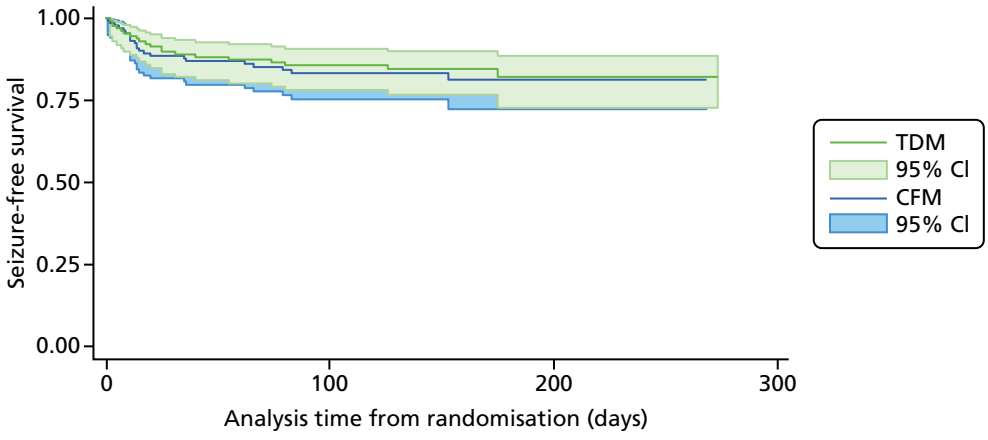

FIGURE 6 Survival graph for time to first event analysis on tonic–clonic seizure only. CFM, clinical features monitoring; TDM, therapeutic drug monitoring.

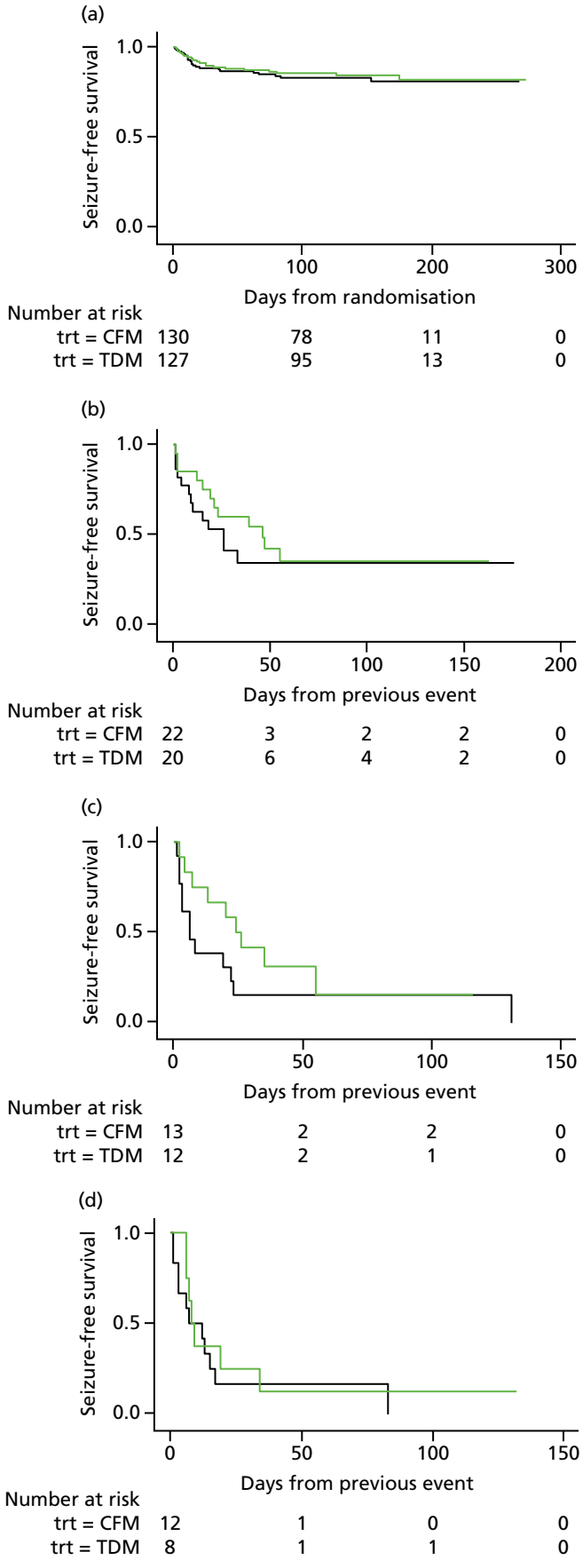

FIGURE 7 Survival graphs for time to first tonic–clonic seizure and time to subsequent tonic–clonic seizures. Time to (a) event 1; (b) event 2; (c) event 3; and (d) event 4. CFM, clinical features monitoring; TCS, tonic–clonic seizure; TDM, therapeutic drug monitoring; trt, treatment allocation.

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The analysis of time to first and subsequent tonic–clonic seizures showed a decrease with therapeutic drug monitoring compared with clinical features monitoring, which was not significant (*Table 8*; HR 0.62, 95% CI 0.28 to 1.4).

Effects of monitoring strategies on maternal and fetal outcomes

Maternal outcomes

Pregnancy outcomes

There were no differences between the therapeutic drug monitoring or clinical features monitoring groups in mean gestational age at delivery, pre-term birth rate, mode of delivery, rates of ante- or postpartum haemorrhage or admission to a neonatal unit or rate of breastfeeding (*Table 9*).

TABLE 8 Sensitivity analysis: multiple failure times on tonic–clonic seizure only

		Analysis time (days), mean (SD)		Number of seizure days, mean (SD)		
Model	*n*	TDM	CFM	TDM	CFM	TDM effect, HR (95% CI)
Multiple seizure rate	257	149 (50)	130 (55)	0.54 (1.9)	0.84 (3.2)	0.621 (0.28 to 1.4)

CFM, clinical features monitoring; TCS, tonic–clonic seizure; TDM, therapeutic drug monitoring.

TABLE 9 Effect of AED monitoring strategies on maternal outcomes

	Randomised group, *n* (%) [*N*]		TDM effect	
Maternal outcome	TDM	CFM	OR (95% CI)	MD (95% CI)
Maternal death	0 (0) [130]	0 (0) [133]		–
Gestational age at delivery (weeks), mean (SD) [*n*]	39.2 (2.1) [126]	39.1 (2.4) [130]		0.84 (–3.0 to 4.7)
Mode of delivery (effect of CS or instrumental)			1.3 (0.78 to 2.1)	
Pre-term delivery at < 37 weeks	8 (6) [127]	15 (12) [130]	0.50 (0.20 to 1.2)	
Induction of labour	46 (37) [126]	39 (30) [130]	1.4 (0.79 to 2.3)	
Pre-eclampsia	5 (4) [126]	4 (3) [130]	1.4 (0.36 to 5.7)	
Gestational diabetes mellitus	9 (7) [126]	3 (2) [130]	3.2 (0.85 to 12.5)	
Antepartum haemorrhage	2 (2) [127]	2 (2) [129]	1.1 (0.14 to 8.7)	
Postpartum haemorrhage	19 (15) [127]	18 (14) [130]	1.1 (0.55 to 2.3)	
Admission to HDU or ICU	5 (4) [127]	3 (2) [130]	1.8 (0.41 to 7.8)	
Breastfeeding	[127]	[126]	0.82 (0.50 to 1.4)	
Breast	75 (58)	69 (52)		
Mixed	15 (12)	20 (15)		
Bottle	36 (28)	38 (29)		

CFM, clinical features monitoring; CS, caesarean section; HDU, high-dependency unit; ICU, intensive care unit; MD, mean difference; OR, odds ratio; TDM, therapeutic drug monitoring.

Maternal exposure to antiepileptic drugs and rates of seizures

One woman received phenytoin monotherapy and one woman received lamotrigine polytherapy with carbamazepine. There were no differences between the therapeutic drug monitoring and clinical features monitoring groups in the mean daily dose of AEDs prescribed (monotherapy or polytherapy) (*Table 10*). *Appendix 2* shows the effect of increasing the dose of AEDs in women taking monotherapy and polytherapy, and found no significant effect on maternal pregnancy outcomes.

Fetal outcomes

There were no neonatal deaths in any of the randomised women and two stillbirths in the clinical features monitoring group. The odds of major congenital malformations, small for gestational age fetuses and admission to the neonatal unit did not differ between the two groups (*Table 11*). We did not observe any differences in birthweight, head circumference, Apgar scores at 1 and 5 minutes, and cord arterial and venous pH of infants born to mothers exposed to therapeutic drug monitoring or clinical features monitoring strategies. The cord blood levels of the AEDs were available for babies born to women taking lamotrigine ($n = 131$), carbamazepine ($n = 26$) and levetiracetam ($n = 66$). We observed a significant increase in the cord blood levels of lamotrigine [mean difference (MD) 0.55 mg/l, 95% CI 0.11 to 1.0 mg/l) and levetiracetam (MD 7.8 mg/l, 95% CI 0.86 to 14.8 mg/l) in infants born to mothers managed in the therapeutic drug monitoring group compared with in the clinical features monitoring group. There were no differences in cord blood levels of carbamazepine (MD –0.47 mg/l, 95% CI 1.5 to 0.60 mg/l) between the two groups. We quantify the effect of an increase in AED dose on fetal outcomes in *Appendix 3*. An increase in exposure to AED dose by 1 mg significantly increased the cord blood levels of lamotrigine, by 0.007 mg/l (see *Appendix 3*), levetiracetam, by 0.008 mg/l, and carbamazepine, by 0.003 mg/l, in women on AED monotherapy. The cord blood levels of lamotrigine and levetiracetam were increased by 0.009 and 0.008 mg/l, respectively, for every 1-mg increase in dose of AED in women on polytherapy. The cord blood venous pH was significantly reduced by –0.0002 per 1-unit increase in dose of carbamazepine, but there were no effects on other fetal outcomes with increasing doses of AED (see *Appendix 3*).

Maternal quality of life

Table 12 compares the QoL measurements in mothers exposed to the two AED monitoring strategies. There were no differences in the EQ-5D postnatal scores between the two groups (MD 0.002, 95% CI –0.05 to 0.05). The scores for the QOLIE-31 and the overall health score were similar in both groups (see *Table 12*).

Effect of a reduction in serum antiepileptic drug levels on maternal seizures

Table 13 compares the seizure status between women in the non-randomised group with stable serum AED levels and women in the clinical features monitoring and therapeutic drug monitoring groups with a decrease in serum AED levels of > 25%. There were no significant differences between the groups in seizure status, which was adjusted for baseline seizures in the 3 months prior to pregnancy.

TABLE 10 Differences in dose of AED exposure between the therapeutic drug monitoring and clinical features monitoring strategies

AED	Daily AED exposure (mg), mean (SD) [*n*]		TDM effect, mean difference (95% CI)
	TDM	CFM	
CBZ only	616.7 (355.8) [16]	695.0 (336.4) [20]	–12.1 (–226.7 to 202.4)
LTG only	290.9 (137.5) [68]	252.6 (148.0) [70]	32.3 (–14.4 to 79.0)
LEV only	1735.6 (701.9) [31]	1628.5 (926.5) [31]	166.5 (–229.8 to 562.7)
LTG and LEV	LTG: 487.5 (206.7); LEV: 1920.1 (858.9) [11]	LTG: 413.8 (91.1); LEV: 2122.2 (1077.5) [14]	LTG: 97.4 (–28.7 to 223.4); LEV: –137.3 (–945.9 to 671.4)

CBZ, carbamazepine; CFM, clinical features monitoring; LEV, levetiracetam; LTG, lamotrigine; TDM, therapeutic drug monitoring.

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TABLE 11 Effect of AED monitoring strategies on fetal outcomes

Fetal outcomes	Randomised group, *n* (%) [*N*]		TDM effect	
	TDM	CFM	OR (95% CI)	MD (95% CI)
Stillbirths	0 (0) [125]	2 (2) [134]	–	–
Neonatal deaths	0 (0) [126]	0 (0) [134]		–
Major congenital malformations	7.0 (6) [125]	10.0 (8) [134]	0.66 (0.23 to 1.8)	
Admission to neonatal unit	16.0 (13) [125]	18.0 (13) [134]	1.6 (0.29 to 9.5)	
Apgar score at 1 minute, mean (SD) [*n*]	8.5 (1.4) [123]	8.5 (1.5) [127]	–	–0.11 (–0.47 to 0.25)
Apgar score at 5 minutes, mean (SD) [*n*]	9.4 (0.87) [124]	9.3 (0.84) [128]	–	0.03 (–0.18 to 0.23)
Birthweight (kg), mean (SD) [*n*]	3.3 (0.60) [124]	3.3 (0.68) [134]	–	0.02 (–0.13 to 0.17)
Small for gestational age fetus (birthweight < 10th centile)	13.0 (11) [124]	22 (16) [134]	0.43 (0.08 to 2.3)	
Head circumference (cm), mean (SD) [*n*]	34.2 (1.8) [104]	34.2 (1.7) [108]		–0.16 (–0.60 to 0.27)
Cord arterial pH, mean (SD) [*n*]	7.3 (0.09) [55]	7.2 (0.07) [46]		0.01 (–0.02 to 0.04)
Cord venous pH, mean (SD) [*n*]	7.3 (0.08) [59]	7.3 (0.07) [54]		0.001 (–0.030 to 0.031)
Cord blood levels CBZ (mg/l), mean (SD) [*n*]	3.3 (1.5) [13]	4.3 (1.3) [13]		–0.47 (–1.5 to 0.6)
Cord blood levels LTG (mg/l), mean (SD) [*n*]	2.5 (1.6) [63]	1.9 (1.3) [68]		0.55 (0.11 to 1.0)
Cord blood levels LEV (mg/l), mean (SD) [*n*]	22.5 (17.0) [30]	13.9 (10.5) [36]		7.8 (0.86 to 14.8)

CBZ, carbamazepine; CFM, clinical features monitoring; LEV, levetiracetam; LTG, lamotrigine; MD, mean difference; OR, odds ratio; TDM, therapeutic drug monitoring.

TABLE 12 Effects of therapeutic drug monitoring and clinical features monitoring strategies on maternal QoL

Outcome	Randomised group, mean (SD) [*n*]		
	TDM	CFM	MD[a] (95% CI)
EQ-5D score	0.90 (0.20) [99]	0.90 (0.18) [102]	0.00 (–0.05 to 0.05)
QOLIE-31 score (UK)	71.0 (16.0) [114]	73.7 (13.5) [110]	–2.5 (–5.1 to 0.0)
QOLIE-31 overall health (UK)	6.9 (1.8) [115]	7.3 (1.6) [110]	–0.35 (–0.72 to 0.02)

CFM, clinical features monitoring; TDM, therapeutic drug monitoring.
a Models are adjusted for baseline values in addition to adjustment factors included in all models.

TABLE 13 Seizure status by end of follow-up compared with baseline

Group	*N*	Seizure status at end of follow-up, *n* (%)		OR (95% CI)
		No seizures	Any seizures	
Non-randomised cohort (decrease in serum AED level never exceeding 25%)	263	140 (53)	123 (47)	Reference group
CFM (decrease in serum AED level exceeding 25%)	130	71 (55)	59 (45)	0.93 (0.56 to 1.5)
TDM (decrease in serum AED level exceeding 25%)	132	74 (56)	58 (44)	0.93 (0.56 to 1.5)

CFM, clinical features monitoring; OR, odds ratio; TDM, therapeutic drug monitoring.

Table 14 shows that there were no differences in the average number of seizures per week and the average number of days with seizures per week, analysed using Poisson models. We removed an extreme outlier who had an average of 256 seizures per week.

Serious adverse outcomes

Sixty-one women experienced one or more serious adverse outcomes between the time of consent and 6 weeks postnatally (*Table 15*).

The most frequent serious adverse event was admission to hospital for seizures, which contributed to 37% of serious adverse events in the therapeutic drug monitoring group, 40% of the serious adverse events in the non-randomised group and almost half of the serious adverse events in the clinical features monitoring group.

Other maternal adverse outcomes made up approximately one-quarter of serious adverse outcomes in each group. Similarly, congenital malformation contributed almost one-quarter to each group, although this was less frequent in the clinical features monitoring group at 18%.

The distribution of serious adverse events did not considerably differ between each group. No serious adverse events were related to the trial.

TABLE 14 Comparison of average seizure frequency between clinical features monitoring and non-randomised participants

Outcome	*n*	Group, median (IQR)		Effect of non-randomised cohort, incident rate ratio (95% CI)
		CFM	Non-randomised	
Seizure rate per week	392	0 (0–0.26)	0 (0–0.26)	1.0 (0.84 to 1.4)
Days with seizures per week	393	0 (0–0.23)	0 (0–0.19)	0.88 (0.62 to 1.2)

CFM, clinical features monitoring.

TABLE 15 Serious adverse outcomes

SAE description	Trial group, *n* (%)		
	Randomised group		
	TDM (*N* = 19)	CFM (*N* = 17)	Non-randomised (*N* = 25)
Admission to HDU/ICU	1 (5)	2 (12)	2 (8)
Admission to hospital for seizures	7 (37)	8 (47)	10 (40)
Admission to neonatal unit	1 (5)	0 (0)	0 (0)
Congenital malformation	5 (26)	3 (18)	6 (24)
Miscarriage	0 (0)	0 (0)	1 (4)
Other fetal adverse outcome[a]	1 (5)	1 (6)	1 (4)
Other maternal adverse outcome[b]	5 (26)	4 (24)	6 (24)

CFM, clinical features monitoring; HDU, high-dependency unit; ITU, intensive care unit; SAE, serious adverse event; TDM, therapeutic drug monitoring.

a Suspected fetal anaemia, spontaneous pneumothorax or infection.

b Postoperative wound infection, suspected cholestasis, bipolar condition, postpartum haemorrhage per vaginal bleed, ankle/fibula injury, intrauterine growth restriction, twins, urinary tract and chest infection, antepartum haemorrhage, minor road traffic accident, slurred speech/facial weakness, stress/psychological evaluation, pulmonary embolism, post epidural head, back, neck and perineal pain, recurrent perianal Crohn's disease, cervical suture or high blood pressure.

Note

Percentages do not add up to 100 as some women may contribute to more than one SAE category.

No SAE was related to the trial.

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Chapter 4 Qualitative study

Introduction

Women with epilepsy who become pregnant possess an expertise on which to base their expectations of pregnancy and childbirth. Their experience of living with epilepsy influences the ways in which they make sense of their pregnancy, as well as their views on the management of the condition. Thus, women's position as 'expert patients' enables them to balance the risks and benefits to themselves and their baby of AEDs within the context of their lives. This chapter reports on the qualitative study undertaken to capture this expertise and to explore in some depth women's lived experiences and perspectives of pregnancy while managing their epilepsy. Qualitative data provide an additional dimension to quantitative results, allowing participants to focus on the issues of importance to them and to explain how they make sense of events within the context of their everyday lives. The growth of qualitative studies within a quantitative randomised controlled trial (RCT) framework is important, especially in trials, such as AntiEpileptic drug Monitoring in PREgnancy (EMPiRE), which are conducted within sensitive settings of maternal and fetal medicine, in which participants may be considered 'vulnerable'.[23] The purpose of this qualitative study is to understand women's lived experiences and perspectives on managing their epilepsy during pregnancy through interviews with both women who choose to accept participation in the RCT as well as those who declined.

Background

To date, research on epilepsy and pregnancy has been largely investigated using quantitative methods, and this is reflected in evidence-based reviews covering the area.[24,25] Expert reviews[26,27] and guidelines[28] on the management of epilepsy in pregnancy focus on aspects of care important to health professionals. However, there is a stark absence of research concerning the priorities and perspectives of patients themselves.

A review of qualitative literature[29] in this area was conducted in 2013 and found only one study[30] that directly investigated women's experiences of epilepsy during pregnancy. This 'exploratory qualitative' study, carried out by Thompson *et al.*,[30] investigated the experiences of women living with epilepsy of health-care services at key phases of reproduction, including contraception, pre-conceptual care, pregnancy, birth and breastfeeding, and parenting and child safety. Women reported mixed experiences of health care during these stages: some felt that they had received good care, but others were given inadequate information and offered advice from practitioners only after an event, and, thus, they could not take appropriate preventative action. Thompson *et al.*[30] argue that the management of a chronic illness and reproductive health involves work of a 'moral dimension'. For example, in relation to their pregnancy, the concern with the effects of AEDs on their unborn babies created a conflict for women between being a 'good mother' and being a 'good patient'. Thompson *et al.*'s study[30] provides a much needed contribution to understandings of how epilepsy influences women's experiences of the various stages of pregnancy and reproduction. However, as it is an exploratory study with a small sample size of 15 women, findings remain limited in scope.

The 2013 literature review[29] included studies exploring not only women's experiences of pregnancy, but also their experiences of reproductive health while managing epilepsy. This expansion of the review resulted in 16 additional publications, which were limited in their generalisability because of the small sample sizes and/or poor quality of data. Since the publication of this review, one additional study has been published in this area: Qiang *et al.*'s 2016[31] small qualitative study on the support networks of 12 pregnant women living with epilepsy. There is, therefore, a dearth of high-quality research on the experiences of pregnant women living with epilepsy.

Study aim

To investigate the perspectives and experiences of pregnant women living with, and managing, epilepsy.

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Objectives

To gain insight into the way pregnant women with epilepsy rationalise and make sense of the management of AEDs in the context of their lives by addressing the following research questions:

- How do women experience living with epilepsy before becoming pregnant?
- What do women perceive as issues of concern for them and their baby in terms of epilepsy management during pregnancy and childbirth?
- How do women construct and make sense of the risks, and benefits, for themselves and for their baby in terms of medication?
- How do women perceive maternal responsibility in the context of having epilepsy?
- What and who influences women's decision-making in the management of their condition during pregnancy?
- How do women view their experience of pregnancy and childbirth and the management of their medication during this time?

Methodology

The above research questions were explored empirically through semistructured interviews using participant narratives.[32] This approach allowed research participants some control in the research agenda as they could focus on issues that were of concern to them and elaborate in order to provide context and rationales for the ways in which they make sense of managing their epilepsy over the course of a pregnancy. Reporting was undertaken in line with recommended guidelines.[33]

Sample

Theoretical sampling was employed to purposely include women from different geographical regions, with a diversity of sociocultural backgrounds, and who had varied histories with epilepsy and had experienced a range of neurological symptoms. A total of 32 women participated in interviews, of whom 21 had enrolled in the RCT and 11 had declined the trial but agreed to take part in the qualitative study. Recruitment and sampling continued until data saturation was reached and no further analytical categories emerged from ongoing analysis of interview data.[34] Saturation was determined independently by the EMPiRE trial qualitative lead, Elaine Denny, and research fellow, Annalise Weckesser. Women were first approached face to face by research nurses and midwives and given informed consent forms for the qualitative study. Annalise Weckesser then telephoned women who had agreed to take part in the qualitative study and who had signed informed consent forms.

Method

The aim of this research was to gain insight into the way women make sense of living with epilepsy during pregnancy and, thus, a qualitative approach was appropriate. All women were requested to take part in two or three interviews, which were audio-recorded with their permission and transcribed verbatim. Annalise Weckesser or Elaine Denny interviewed the women twice. Annalise Weckesser and Elaine Denny are both women with experience conducting qualitative research. The interviewers did not establish relationships with participants prior to the commencement of the study. Participants knew that Annalise Weckesser and Elaine Denny were non-clinical members of the EMPiRE trial research team, and that both have research interests in gender, reproductive health and chronic illness.

The first interviews took place when women were pregnant and had either entered the trial or refused to enter the trial. The second interviews took place approximately 6 weeks after participants had given birth. First interviews lasted approximately 1 hour and second interviews lasted approximately half an hour. Eight women did not participate in follow-up postnatal interviews: one returned to her country of origin, two withdrew from the RCT and five were unable to be contacted.

Interviews were conducted at places and times convenient to participants. The majority of women were interviewed in their own homes; however, some preferred to be interviewed at hospitals after their antenatal clinic appointments and some interviews took place over the telephone. Most women were interviewed on their own; however, some women asked for their partner ($n = 4$) or mother ($n = 2$) to be present to help them remember details of their seizures and medication. Most postnatal interviews were conducted over the telephone as this was most convenient for women with the time constraints of caring for their newborn. In appreciation for their time and participation, women were given a £20 gift voucher following completion of their first interview.

First interviews took place on the women's entry to or refusal of the randomised trial, and these interviews focused on the six research questions (see *Objectives*). Additional interviews were originally proposed with women in the qualitative study who had experienced a reduction in serum AED level or who experienced a seizure during pregnancy to explore if these events altered patients' perspectives on epilepsy and pregnancy and raised new concerns. However, this was not possible as research nurses and midwives did not inform Annalise Weckesser and Elaine Denny when a patient had a seizure during pregnancy. However, in postnatal interviews, Annalise Weckesser and Elaine Denny learned that some participants did have seizures during their pregnancy and we were able to capture these experiences retrospectively. Postnatal interviews concentrated on women's reflections on the research questions on the presumption that pregnancy experiences can only be fully reflected on once the outcome of the pregnancy is known. Short field notes were taken immediately after the first and second interviews to make note of, and describe, where interviews took place.

Elaine Denny and Annalise Weckesser developed interview guides to ensure data collection on relevant topics (see *Appendix 4*), but participants were also free to raise issues of importance to them. The interview guide was developed based on themes identified in a review of qualitative literature on the experiences of pregnancy and reproductive health of women living with epilepsy, which was published by Elaine Denny and Annalise Weckesser in 2013.[29] Basic demographic data including current age, parity and years living with epilepsy were collected from participants at the beginning of the first interview.

Ethical considerations

As epilepsy is considered to be a stigmatising condition,[35] the researchers avoided stereotyping and discriminatory use of language. Each woman's guidance was sought at the beginning of interviews concerning acceptable use of terminology. The researchers complied with the British Sociological Association's statement of ethical practice.[36] Pseudonyms have been used to protect the anonymity of participants.

Analysis

A narrative analysis was adopted as this method has much to contribute to studies of chronic illness. As Riessman notes, '[t]elling narratives is a major way that individuals make sense of disruptive events [such as illness] in their lives'.[37] Within this narrative mode of analysis, a thematic approach was undertaken – a method that allowed for the identification of common themes across cases while enabling individual women's stories to remain intact.[38] To ensure rigour in the analysis process and to establish trustworthiness in the findings, Elaine Denny, Annalise Weckesser and a member of the EMPiRE trial team read all interview transcriptions. Annalise Weckesser took the lead in developing the analysis to increase internal consistency, but all members agreed on coding frames and analytical themes for internal validity. Annalise Weckesser created a coding frame for categorisation of data using NVivo 10 (QSR International, Warrington, UK). Analytical themes and concepts were developed and explored using the constant comparison method.[39] An additional strand of narrative analysis was also conducted, allowing for the integrity of each woman's interview to be maintained.[38] This analysis of narratives allowed for an understanding of the inter-relatedness of a person's life story that can be lost and fragmented in the constant comparison method.[38] These two methods of analysis provided insights into how women experience pregnancy and epilepsy, and how they make sense of these events within the context of their lives.

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Findings

Sample results

Participants came from urban areas, including London, Birmingham, Cardiff and Liverpool, as well as more rural areas such as Shrewsbury, Gwent and Worcestershire. *Table 16* provides the sociodemographic details of participating women. At the time women were first interviewed, over half were becoming mothers for the first time ($n = 18$) and the rest had at least one child. The youngest participant was aged

TABLE 16 Sociodemographic background of the study sample ($N = 32$)

Demographic	Number of participants
Age (years)	
Range	19–42
Mean	31
Marital status	
Married	18
Cohabiting	10
Non-cohabiting/with partner	2
Single	2
Parity	
Primigravida	18
Gravida 2, parity 1	10
Gravida 3, parity 2	4
Employment	
Professional	17
Retail	2
Student	1
Unemployed/full-time mother	12
Ethnicity	
White British	21
British Asian	4
White European	1
White American	1
Black African	1
Chinese	1
British black Caribbean	1
Years with epilepsy	
Range	1–29
Mean	11.2
Types of seizures[a]	
One-off seizure	1
Absence seizures	9
Myoclonic	9
TCS (self-defined)	17

TCS, tonic–clonic seizure.
a Some women report more than one type.

19 years and the oldest was aged 42 years (mean age 31 years). More than half of participants were married ($n = 18$) and others lived with partners ($n = 10$), lived separate from partners ($n = 2$) or were single ($n = 2$). Women worked in professional occupations ($n = 17$) and in retail ($n = 2$), or were unemployed and/or full-time mothers ($n = 12$); one was a full-time student. The majority of participants had been born in the UK and self-identified as white British ($n = 21$); others identified as British Asian ($n = 4$) and British black Caribbean ($n = 1$). A number of women had immigrated to the UK, including three participants who identified as white European and one each as Chinese, black African and white American. One NHS Mandarin interpreter was required to provide an interview translation.

Participants had varied histories with epilepsy. One mother was diagnosed only within the past year and, at the other end of the spectrum, a participant had lived with the condition for 29 years. On average, women had lived with their condition for 11 years. Women also experienced a wide range of neurological symptoms. Participants self-identified their seizure types, ranging from tonic–clonic seizures (which constitute the more popular images of epileptic convulsive seizures with a person losing consciousness, their muscles stiffening and jerking), myoclonic seizures (involving the brief, shock-like jerking of muscles) and absence seizures (which are absences in awareness and women often described these experiences like 'déjà vu' or an 'aura'). Some women experienced more than one type of seizure at different stages in their life, and the frequency of seizures also differed between women and among individual women over time.

Interview findings

The following findings are based on ante- and postnatal interviews. For the purposes of this chapter, findings are presented thematically rather than as narrative case studies to facilitate the reporting of findings related to the qualitative study's research objectives of understanding:

- women's experiences of living with epilepsy before becoming pregnant
- women's concerns in relation to epilepsy management in pregnancy
- women's strategies for balancing risks and benefits to themselves and their babies in relation to medication
- women's perceptions of maternal responsibility in the context of having epilepsy
- the influences on women's decision-making in the management of epilepsy and pregnancy
- women's postnatal reflections on the experience of pregnancy and childbirth, and the management of epilepsy
- women's reasons for declining trial participation (for participants who declined participation in the randomised trial).

Although reporting findings through this separation of strands of experiences brings clarity, it must be noted that it creates a false distinction; in reality, people's experiences, feelings and actions are interlinked and, thus, cannot be easily reduced to simple, segregated categories.

Experiences of living with epilepsy before becoming pregnant

Women's histories of living with epilepsy before becoming pregnant are highly diverse. This diversity is reflected in the spectrum of seizure types and frequencies experienced by participants, and the number of years they have lived with the condition (see *Table 16*). Although some women had been diagnosed in childhood, others did not receive a diagnosis until more recently and/or after a first pregnancy.

With regard to how the management of their condition impacted on day-to-day life, women's responses ranged and were shaped by this diversity of seizure types and frequencies. For some, the fear of having a seizure was a daily occurrence:

> *[I] feel quite nervous and self-conscious all the time because I don't know when I'm going to have my next seizure.*
>
> *Cecilia*

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For some, epilepsy impacted on their work and chosen career paths. For example, one participant reported losing her job in a factory after her diagnosis as she was not allowed to work near the machinery in case she should have a seizure. Another participant had been training as a beautician but was told she could not continue with the course after disclosing her diagnosis, as she would not be allowed to use some of the electrolysis machines.

The majority of participants, however, reported that on a day-to-day basis their condition did not impact on them greatly. Some made modifications to their lifestyle (ensuring that they get enough sleep, refraining from excessive alcohol consumption, not bathing alone, etc.) but saw these as minor adjustments. Riva is one such woman; despite these adjustments, she states that she leads a 'normal life':

> *[Prior to becoming pregnant] I could get up every day, I would have my medication, I could go to work and have a normal life and go back home. And you know, it wasn't something that would impact me greatly . . . I had a gap of several years between my seizures. So for me the seizures, like it didn't feel like it had a particularly detrimental impact on my life.*

Other participants had such infrequent seizures, some having ever experienced only one seizure, that they reported not feeling they had 'real epilepsy' and that they were 'lucky' as they believed they faced less hardship and stigma than those with less controlled and more 'severe' seizures.

In addition to the diversity of epilepsy experiences, some participants faced additional pregnancy and/or concurrent health concerns that took primacy over their epilepsy. Some women reported fertility issues, challenges having a baby in their forties, undergoing in vitro fertilisation treatments and/or having past experiences of miscarriage. Becoming pregnant was reported, by some, to be more of a challenge and concern than managing their epilepsy:

> *I thought, 'OK, I just need to manage my medication and then I'll get pregnant' . . . I think more than anything to do with my medication that was the biggest shock for me, that actually it isn't that easy to get pregnant. Like it's easy to manage what dosage you take and to keep tabs on what you're taking, making sure you go and see the specialist and [your epilepsy is] managed. But I think the biggest shock to me was just the process of actually getting pregnant in the first place.*
>
> *Sonia*

Other participants reported additional health concerns that impacted on their day-to-day life, including Tourette syndrome, congenital talipes equinovarus, overactive thyroid and high blood pressure, as well as other related health issues that arose during pregnancy, such as pre-eclampsia and gestational diabetes. One participant felt that managing her Tourette's affected her more than her epilepsy:

> *The epilepsy I don't notice, because if I have a fit, it's always at night time. So I've never had one in the day, I've always been fine. Because in the day, I kind of control the Tourette's.*
>
> *Tanya*

Women's experiences of epilepsy were also influenced by their different sociocultural and religious backgrounds. One participant believed that her epilepsy had been caused by a curse and attended evangelical faith healing sessions. Another participant, Amina (aged 31 years), after being diagnosed with the condition reported becoming a more 'devout' practising Muslim, signified by adopting a hijab. Amina believes that her faith helps her manage her condition; however, she continues to take her AEDs:

> *I've got my religion, but I've also got the doctors. This medication's there for a reason. It's helped me not have a seizure all this time so I'll just continue.*

Women's experiences of living with epilepsy prior to becoming pregnant are highly diverse and are shaped by their particular seizure type(s) and history, whether or not they have additional health and fertility concerns and their sociocultural backgrounds.

Concerns in relation to epilepsy management and pregnancy

As discussed in the previous section, for many participants the everyday management of epilepsy prior to becoming pregnant had become routine and normalised. However, pregnancy often becomes a stage at which women have to reflect on their condition and how it impacts on their health and that of their baby. This is illustrated by the case of Philomena (aged 31 years), who states that before becoming pregnant she 'wasn't thinking about [her epilepsy] from one day to the next . . .'. After first being diagnosed, she initially took on 'all the good habits'. She continues:

> *I never used to drink . . . [I] only took a bath when people were there. So you kind of start with really good practices . . . [A]nd then as the years go by you just stop thinking about it completely and you just take your tablets every night and you're fine . . . But then as soon as you became pregnant you need to get back into good habits . . . [W]hen you have the baby you need to change [them] on the floor, you shouldn't do this, you shouldn't do that, and you were just a bit like, 'Oh yeah, I completely forgot!'.*

Thus, pregnancy is a time that raises many concerns for women living with epilepsy, concerns about things that some may have previously taken for granted.

Participants reported that their primary concern was to give birth to a healthy baby, with no abnormalities:

> *I think really you worry about everything, you could worry about anything, but I think the main thing is I just want to have a happy and healthy baby at the end of it.*
>
> *Simone*

> *At the moment I get concerned about whether [the baby's] going to be normal or not. Otherwise, I haven't got any concerns.*
>
> *Mary*

> *The first question I'm asked is, 'Do you want a girl or a boy?'. And I just say, 'I want a normal baby'. A healthy, normal baby . . . I don't care whether it's a girl or a boy . . . I hope it's a healthy, fat baby.*
>
> *Samina*

Women also expressed concerns about the effects of their AEDs on their unborn babies. Although participants often reported feeling some reassurance from health practitioners who advised them that the medication they were on were newer AEDs believed to be safer during pregnancy, some still had concerns about possible teratogenic effects, including spina bifida and learning disabilities. This is illustrated in the following extract:

> *The doctors are like 'Oh this is a great drug, it's much better than the one you were on before'. And I'm thinking, 'Yes, but the one I was on before it's been around 20, 30 years'. So you know that there's defects, but you know at what levels those defects occur and how likely it is to happen. Whereas you put me on this new medication, which actually has been around maybe 4 or 5 years so you have a little bit of experience . . . Even though [the doctors'] experience and knowledge is quite valid, but at the same time they don't have to live with the consequences of it.*
>
> *Riva*

Some women were concerned that they could pass their condition on to their babies, despite the knowledge that genetic inheritance of epilepsy is very rare:

> *The other thing that you worry about is sometimes it's like I hope [epilepsy's] not something I can pass on to my baby because I really wouldn't want that . . . Even though they say it's not inherited you just don't know because they say some forms can be.*
>
> *Fatimah*

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Women also expressed concerns about having a seizure during their pregnancy, labour and/or in the early postnatal period. During pregnancy, women were especially concerned about having a seizure in their final trimester, when the baby is seen to be more 'fully formed'. As Li Min stated:

> *[I'm] worried that [I'm] going to have a seizure towards the end, when the baby's like mature . . . [I'm] really scared that it's going to happen and it's going to affect the baby and me as well.*

Participants worried that a seizure could cause a decrease in the amount of oxygen that gets to the fetus. Tiredness and stress during pregnancy and from the strains of giving birth were also seen as possible seizure triggers. For example, one participant, Laura, feared that she was more likely to have a seizure in her current pregnancy than in her former, as she was now experiencing more sleeplessness as a result of taking care of her firstborn, who was still a baby:

> *I think I'm probably more concerned this time round because I have it in the back of my mind that I'll probably have more seizures during this pregnancy because of having [my son] and the sort of stress of looking after him really, as well as the tiredness . . . [T]he end of the day comes and you think 'I don't think I've even brushed my teeth today to start off with' . . . So I'm more concerned that I'm going to be more tired, which will lead to me having more seizures, which will lead to me being more tired.*

Finally, women were very concerned about having a seizure because this could result in losing driving privileges until they have been seizure free for 1 year:

> *The main hope is not to have any déjà vu. Because even the slightest déjà vu I need to inform [my medical team] . . . So that is a worry, but mainly for the selfish reasons of driving.*
>
> *Laura*

> *[If I have a seizure] then I wouldn't be able to drive, which I think would be a massive issue . . . [T]hat would make everything like a million per cent more difficult.*
>
> *Philomena*

Women in rural areas with little public transport and those who required a vehicle for work were especially concerned about the isolation and inconveniences caused by losing their driver's licence in the event of a seizure.

Strategies for balancing risks and benefits to themselves and their babies in relation to medication

Many of the participants reported thinking about whether or not they should have children in view of having epilepsy. Most women had planned their pregnancies ($n = 22$) and two women had been advised against having children because of their condition (one by a doctor and one by their partner). Philomena reflects on her decision to have a baby, stating:

> *You think about what effects the drugs have on the baby, what if I had a fit . . . There are all of those considerations, but for me none of them outweighs actually having a baby.*

In relation to taking AEDs, women made their medication management decisions by weighing up the risks to the health of their baby, their own health and other aspects of their life. Some women felt it was particularly important to keep taking their medication during their pregnancy to minimise the risk of seizures:

> *I can't help but think I'm so scared that I'll have a seizure and somehow or another I will end up hurting either the baby or myself . . . And I think your priorities completely change, you do want to do what is best for your baby, but at the same time if you're harming yourself you can't be doing what's*

right for your baby. If I fall and if I have a seizure, then I'm risking both anyway. I think you've just got to look at it practically.

Fatimah

The risk of me being on the medication is minimal [to the baby] . . . But the risk of me falling down a flight of stairs could kill her really.

Shelly

Thus, although participants saw continuing their AEDs during pregnancy as potentially harmful to the health of their babies, such risks had to be balanced with what some saw as a more likely and harmful risk of having a seizure that could occur if they stopped or reduced their medication. Some women did choose to stop or reduce their medication in the first trimester because of the perception that the fetus was at heightened risk of malformations at this time:

When I found out I was pregnant with [my first child], I did stop taking [the medication] 'til after my 3-month scan, and I did do this time as well for the current pregnancy . . . I went to the [clinic] at about 10 weeks' pregnant and [the epilepsy nurse] said, 'Have you had any seizures?'. I said, 'No'. She said, 'You know you're more susceptible, etc., etc.?'. And I said, 'Yes'. And she said, 'Well I'm going to leave you to it'. And then 10 days later I had a bout of seizures, so that just brought me up to my 12-week scan, so I'm back on my medication now, properly.

Laura

Women's decisions about taking medication in pregnancy to prevent seizures had to be balanced with other aspects of their lives, such as the need to keep their driving licence. One participant, Sandra, had a seizure during her first pregnancy, and during her second pregnancy she stated:

[The seizure] cost me my driving licence. I was a community midwife [in a rural area] . . . It was the most depressing time without a driving licence. I didn't really know how much it meant to me, and it put me off getting pregnant again because the thought of losing my driving licence again, it was too much of a risk.

Sandra

Sandra believed she had the seizure because her epilepsy specialist midwife had failed to increase her AED dosage during the first pregnancy. She reported that for this current pregnancy her epilepsy specialist midwife had agreed to increase her medication, but if the midwife had not, Sandra would have self-managed her medication and increased her dosage to prevent a seizure.

Perceptions of maternal responsibility in the context of having epilepsy

Although women's decisions ranged from stopping, reducing, maintaining and increasing their AEDs over the course of their pregnancies, overwhelmingly the rationale for such decisions was based on a feeling of maternal responsibility towards their babies. This is illustrated in the following two contrasting extracts, one from a woman discussing her decision not to take her AEDs in the first trimester, and one woman on why she continues to take her medication during her pregnancy:

If I took the tablets all the time and something happened and [the baby] comes out deformed in some way or had something wrong with it, then I would think that I've been a selfish person and feel terrible for doing that when I know I can cope for so long without them.

Mary, on not taking AEDs

[T]here is the odd night I'll get into bed and every night [think] 'have you taken your tablets? Yes'. But I will remember if I lay there long enough. I'm like, 'Oh, I didn't take them'. But it's not just me I'm thinking about now. So yes, it is a little bit more important. Because I'm not just taking them for me.

Veronica, on taking AEDs

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Both women made decisions regarding their medication based on feelings of maternal responsibilities towards their unborn children. The types of seizures that the women experienced also informed their choices. Prior to having full tonic–clonic seizures, Mary would often experience symptoms including auras. Thus, if she had any of these early warning signs she would take her medication. In contrast, Veronica did not have such warning symptoms prior to having a seizure.

Women continuing or increasing their medication to prevent seizures in pregnancy still had concerns about the chance AEDs could affect their baby's health. These concerns derived from their role as mothers and carers, now looking after the health of their unborn child as well their own. Clara stated, regarding the possible teratogenic effects, that:

> *[C]hances are very, very low, but then there's always still that chance. And it's not just you that you're talking about any more, it's an extra person, which took me by surprise at how differently I probably feel about that because, you're like, it's not just me any more, it's another little person.*

Participants' feelings of maternal responsibility were also evident in the form of guilt associated with the possibility of having a baby born with health problems, as illustrated in the following extract:

> *I worried a lot that if there were problems with the baby that it would be my fault. It wouldn't necessarily be my fault, but it kind of is if you know what I mean. I worried that the drugs that I took . . . I did have quite sleepless nights thinking, 'Oh God, what if something happens to the baby and they're born with defects that I'm going to have to explain to it'. That worries me.*
>
> *Nicole*

Influences on decision-making in the management of epilepsy and pregnancy

Women had a range of influences on their decision-making in the management of epilepsy and pregnancy. In relation to their medication, many made decisions regarding their dosage in consultation with their neurologist, epilepsy nurse or epilepsy midwife, but were also informed by knowledge of their own body, history with the condition and seizure warning symptoms. Women's decisions, as discussed in *Perceptions of maternal responsibility in the context of having epilepsy*, were also shaped by considerations for the well-being of their baby. Many participants had partners and key family members (such as mothers) who provided them with care and support in the management of their condition. However, partners and family members did not play key roles in influencing women's AED management choices. As Fiona replied, in relation to her medication, 'At the end of the day I make the decisions for what I want and what's best for me and the child'.

Some women reported using the internet to research the teratogenic effects of the particular AEDs they took, but viewed such information as supplementary to the professional advice of their medical team.

Postnatal reflections on the experience of pregnancy and childbirth, and the management of epilepsy

Women's perspectives on pregnancy and managing epilepsy were shaped by labour and pregnancy outcomes. The majority of women reported giving birth to babies who, from birth to the point of the postnatal interview, did not have any apparent health problems linked to taking AEDs. For such women, their views on having a pregnancy while managing epilepsy were largely positive. This is reflected by Jeannette, who stated, 6 weeks after giving birth to a healthy baby:

> *I just don't think if a woman has epilepsy [that she] should be scared to have a baby because [she] could be like me, everything is fine, no worries at all. So I wouldn't even worry about thinking, 'Oh I can't have a baby because I've got epilepsy'. Because it's twaddle really.*

One participant reported early health problems with her baby that she was concerned could be linked to AEDs. Amy had a son 'born with shaky arms and legs' and some possible visual impairment. She stated

that '[At] first, I thought, "Oh was that to do with the medication?" Could that have had an influence because I take these tablets?'. She consulted paediatricians who attributed these complications to an 'immature neurological system' and assured her that her son would 'grow out' of the 'shakes'. Amy stated that she now felt 'pretty reassured' as the doctors did not believe the medication caused her son's health impairments and because she is prescribed 'one of the safest drugs and take[s] quite a relatively low dose'.

Although seizure during labour had been a concern for some women while they were pregnant, only one participant experienced a seizure during childbirth. Many women reported negative experiences in postnatal wards as a result of a lack of sleep and staff shortages. Some women reported feeling 'abandoned' and 'vulnerable' to seizure in the postnatal ward. They expressed a desire for a partner or family member to remain on the ward to help care for them and their newborn infant. Although a few wards allowed partners/family members to remain outside of visiting hours, this was not universally practised across all wards. One woman reported that she felt that she would not have another baby because of her poor postnatal care experience.

In relation to caring for their newborns, many women reported having to make accommodations as a result of their epilepsy. This was evident in sleeping patterns, breastfeeding strategies and day-to-day care practices for infants. For some participants, sleep deprivation was a seizure trigger. Thus, to ensure they had enough sleep, some had partners, family members or night nannies take the lead in baby care and feeding overnight. Some of these women expressed feelings of guilt that they were not 'proper' mothers because they were not doing night feeds.

Many women found mixed feeding (combining breastfeeding and bottle feeding) an effective way to ensure that their babies got the health benefits of breast milk while also being able to 'top up' with formula milk. Women felt that this feeding strategy helped babies sleep for longer periods in the night, allowing women to get more sleep. Bottle feeding also allowed partners and family members to share in the feeding duties. A few women reported receiving conflicting advice from health professionals regarding the safety of breastfeeding while taking AEDs.

Precautionary practices in the day-to-day care of newborns, such as breastfeeding or nappy changing while sitting on the floor, refraining from bathing a baby alone and using a car seat when carrying a baby on stairs, were less likely to be taken up by women with a history of well-controlled seizures.

Reasons for declining participation in the randomised trial

Eleven women declined to participate in the RCT. About half ($n = 6$) of this group chose not to take part in the RCT because the randomisation process was not acceptable to them. They were concerned that they may be streamed into the clinical features monitoring strategy of the trial, and would have their medication dosage increased only after a seizure and not when their blood levels decreased, with negative consequences for them and/or their baby. Such women reported that they felt they would lose control over the management of their epilepsy:

> *I thought it would be easier to control my seizures if I didn't go into the study.*
>
> *Clara*

> *For me it would be quite a bizarre choice not to know what was happening to the levels of lamotrigine in my blood, and not to intervene.*
>
> *Sandra*

These six women also expressed concern that they would be at more risk of a seizure if they were randomised:

> *Should I require additional medication, that wouldn't necessarily be prescribed if I was part of the wrong part of the trial.*
>
> *Nicole*

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> *If I could choose which group I was going into that would be fantastic, but I was told I couldn't choose which group I was going into. So it wasn't worth the risk [of having a seizure].*
>
> *Sandra*

The five other non-randomised women chose to decline trial participation for the following reasons:

1. work and time commitments ($n = 1$)
2. lived too far from hospital for required monthly antenatal visits ($n = 1$)
3. fear of needles ($n = 1$)
4. stopped taking AEDs prior to pregnancy and did not want to resume ($n = 1$)
5. believed she did not have epilepsy ($n = 1$).

Discussion

Women sit on a wide spectrum of seizure types and frequencies, and this makes it difficult to categorise women by epilepsy type. The ways in which women made sense of their pregnancy and epilepsy experiences were shaped by both biography and social context. These varied experiences informed the way participants perceived their condition and how they managed their condition before, during and post pregnancy.

Women who experienced relatively few seizures or who had well-controlled seizures often stated that they felt 'lucky' and believed that they faced fewer hardships and stigma than those with more 'severe' or 'real' epilepsy. Overall, participants did not view their epilepsy as a 'disability,' but instead as a chronic health condition that they could manage by taking medication and/or avoiding seizure triggers, including tiredness, excessive alcohol consumption and stress.

For many women, prior to becoming pregnant, the day-to-day management of their condition had become routine and normalised. Pregnancy marked a time when these management routines came to be disrupted. Women had to re-evaluate their drug regime as they now had to consider their increased vulnerability to seizure during pregnancy as well as the risk of teratogenic effects of the AEDs. Women had to weigh up these risks to themselves and to their babies in a context of uncertainty. Risks of seizures and teratogenic effects of medication were possibilities, but not certainties. Participants reported adopting a variety of strategies to mitigate and balance these risks, including reducing, stopping, continuing and increasing their medication during pregnancy. Underlying most of these management strategies was a desire to safeguard the health of their baby.

The findings suggest that a tension may exist between the health professional's focus on drug adherence and the patient's experience of doubt. Women may feel that health professionals have different priorities from them, as it is women who will live with the consequences of drug regimens and any teratogenic effects on their babies. As the findings above show, women experience feelings of maternal guilt and responsibility for their babies being born with any health problems or abnormalities. These findings resonate with those of Thompson *et al.*'s [30] study, which found that women living with epilepsy undertake 'moral work' in relation to their pregnancies and that their concerns with the effects of AEDs on their unborn babies create a conflict between being a 'good mother' and being a 'good patient'.

Strengths and limitations of the qualitative study

As this study was carried out alongside the EMPiRE trial, including only women who chose to have children, there is a risk of bias as those having children may have more well-managed seizures and fewer negative symptoms and side effects associated with their medication. Approximately one-third of women of childbearing age living with epilepsy in the UK consider not having children, or having fewer children, because of their condition.[40]

Additional limitations of this qualitative study include the use of a self-selected sample and an inability to capture participants' experiences of seizure during pregnancy. These seizure experiences were captured only retrospectively through postnatal interviews.

Despite these limitations, the study's strength lies in the original contribution it makes to further understanding women's experiences of epilepsy, pregnancy and reproductive health, in which there has previously been a dearth of robust, in-depth qualitative research.[29] To our knowledge, this constitutes one of only two studies to directly examine women's experiences of pregnancy while managing epilepsy.[30]

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Chapter 5 Discussion

In pregnant women with epilepsy on AEDs, a strategy of additional therapeutic drug monitoring did not significantly reduce the risk of time to first or to multiple seizures compared with management based on clinical features alone. Babies born to mothers who received therapeutic drug monitoring in pregnancy were exposed to significantly high levels of the AEDs lamotrigine and levetiracetam at birth. The average doses of AEDs prescribed in both groups were similar. There were no differences in pregnancy complications, maternal quality-of-life measure, birthweight and breastfeeding rates between the two strategies. The risk of seizure was not greater in the groups whose serum AED levels were reduced than the stable group when the clinical features monitoring and therapeutic drug monitoring groups were compared with the non-randomised cohort. Women's decisions on AED intake and increasing the dose of medication were influenced by concerns for the baby.

The EMPiRE study is the largest randomised trial to date on pregnant women with epilepsy. We recruited women across all four nations in the UK, involving centres that had access to joint obstetric epilepsy care. Our findings are generalisable across the UK for the care of women in the NHS.

Strengths and limitations

We included women on AEDs that are commonly prescribed in pregnancy, with evidence of a reduction in levels in pregnancy, and availability of serum level measurements in the NHS. We excluded women on sodium valproate, as sodium valproate levels in pregnancy are considered to be unreliable, and it is not standard practice in the UK to test sodium valproate levels in (or out of) pregnancy. Our chosen design of early consent, and randomisation only when the serum levels fell, ensured that the data on all the randomised patients contributed to an estimation of the effect, enhancing the statistical power to detect a difference. Follow-up of the non-randomised cohort made it possible for us to blind the control group. Our choice of primary outcome, loss of seizure control, could be defined and analysed in various ways, with no consensus on the best approach.[40] The standard approaches to analysis assume a normal distribution. We expected our data to be highly skewed, with a large proportion (50–60%) of women remaining seizure free throughout pregnancy,[41] and chose time-to-event analysis incorporating estimation of robust standard errors. Since tonic–clonic seizures are considered to be the most severe, we undertook a sensitivity analysis of the primary outcome when limited to only tonic–clonic seizures. By not prespecifying the level of AED in the therapeutic drug monitoring group at which the dose should be increased, we gave clinicians the flexibility to exercise judgement about whether to adjust the AED dose, and to what extent, taking into account patient preferences and factors other than serum AED level that impinge on the decision. The EMPiRE study assessed the effect of two strategies on pregnancy outcomes and is the first trial to assess QoL in mothers with epilepsy on AEDs.

We randomised fewer women than the required target ($n = 660$) to provide definitive evidence on the decrease in time to first seizure by at least 25%. An important clinical effect cannot be ruled out, as indicated by the inclusion of target HR in the confidence limits. We involved units that were able to recruit at least one woman per month and took initiatives to set up joint obstetric epilepsy clinics where none existed before. Owing to our inclusion criteria for recruitment being extended until 24 weeks of pregnancy, it is likely that we may have missed randomising women at an earlier gestation when the levels of AEDs had decreased. Although we preferred to use pre-pregnancy levels of AED as the baseline measure against which to compare future levels to detect any decrease, in practice pre-pregnancy levels of AEDs were rarely available. We accepted serum AED levels at baseline in pregnancy as the alternative, but it is likely that we may have missed the decrease in AEDs in these cases. However, our approach was pragmatic, reflecting current clinical practice, in which clinicians have to rely on first levels in pregnancy as the baseline. Given the small numbers of women on individual AEDs, we refrained from providing separate seizure risks that depended on AED intake. We prespecified a 25% reduction in serum AED level as the threshold for randomising women,

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determined by consensus involving neurologists. It is possible that the effect size would be different for other cut-off points. Although we recruited women from a large number of centres, some centres in the UK refused to participate, as the neurologists from these sites were convinced of the superiority of one strategy over the other. This could be one of the reasons for slow recruitment.

Women's views for declining participation in the randomised trial

Findings from the qualitative study regarding women's rationale for declining the trial may also help understand reasons for slow recruitment. Eleven women who participated in the qualitative study declined the RCT; of these, approximately half reported that they found the process of randomisation unacceptable. They expressed concern that randomisation would lead to a 'loss of control' over the management of their epilepsy as they could potentially be streamed into the clinical features monitoring strategy of the trial, and would have their medication dosage increased only after a seizure and not when their blood levels fell. They believed that not increasing their medication when their blood levels dropped could potentially lead to a seizure and they or their baby could be harmed. Thus, women's concerns regarding preventing seizures in pregnancy and maintaining control over their medication regime could also underpin slow recruitment to the trial.

Reductions in serum antiepileptic drug level in pregnancy and seizure deterioration

Serum AED concentrations often decrease during pregnancy. Physiological changes in pregnancy alter AED pharmacokinetics and AED concentrations. There is reduced gastric tone and motility, and increased plasma volume, renal clearance, albumin levels and protein binding.[9,14,42,43] The reductions in serum AED levels are considered to aggravate seizures.[44] Monitoring of serum AED levels in each trimester and after delivery has been recommended by the American Academy of Neurology based on consensus as a good practice.[44] In the UK, however, the Scottish Intercollegiate Guidelines Network's guideline does not recommend regular AED monitoring in pregnancy because of a paucity of evidence.[12] Our systematic review on the effect of AED monitoring strategies in pregnant women with epilepsy on AED showed lower rates of seizures with therapeutic drug monitoring than clinical features monitoring strategies.[45] The studies were not randomised, or controlled, results were heterogeneous and there was imprecision, with small numbers of women making findings unreliable.

In our trial, we did not observe any differences in seizure rates and time to first and to multiple seizures with the two strategies. Although the point estimates of hazard to time to first seizure and first tonic–clonic seizure, and to multiple tonic–clonic seizures, showed a trend towards favouring therapeutic drug monitoring, the findings were not significant.

Antiepileptic drug exposure in pregnancy to mother and fetus

The measurement of total AED exposure enabled us to delineate the likelihood of excess exposure under therapeutic drug monitoring, in which dose escalation is expected in response to a known decrease in serum AED levels. However, no differences were observed between the groups. It is likely that, when serum AED levels fell, the intervention in the therapeutic drug monitoring group comprised either close monitoring or dose escalation, whereas, without information on serum AED level, clinicians escalated drug doses in response to their clinical monitoring. Despite similar average AED dose exposure in both groups, the cord blood levels of the commonly prescribed AEDs lamotrigine and levetiracetam were higher in newborns in the therapeutic drug monitoring group. The developmental quotient of infants of mothers exposed to lamotrigine in pregnancy compared with women without epilepsy and women not on AEDs appeared to be similar in a small study.[46] There is limited evidence to assess the effect of levetiracetam or AED polytherapy on long-term neurodevelopment.[47]

Quality of life in women using antiepileptic drugs

The effects of seizures extend into daily living, resulting in a loss of driving licence, and are known to have a negative impact on employment and relationships, and reduced QoL.[48] We found no differences in the scores for QoL between the two groups. The additional information on serum AED levels in pregnancy, and the subsequent management based on it, did not appear to adversely affect women's QoL.

Recommendations for clinical practice

Women with epilepsy on AEDs require management in a multidisciplinary setting, with a team involved in both care of their pregnancy and their seizures. The standards of care for individuals with epilepsy vary widely across the UK.[49] This is particularly relevant for pregnant women with epilepsy. Our survey of epilepsy specialists ($n = 29$) in the UK showed that one-third of participants managed women with epilepsy on AED with regular therapeutic monitoring of drug levels, one-third adjusted doses based on clinical features only and the rest used therapeutic drug monitoring occasionally.[50] Given the wide CIs, reflecting the imprecision, the absence of differences between the two strategies and similar rates of seizures in women with stable and reduced serum AED levels, we are not able to advocate routine therapeutic drug monitoring monitoring in pregnancy.

Although we randomised only half the number of women required to provide the definitive answer, given the wide imprecision in the CIs, we do not expect one strategy to be shown to be significantly effective compared with the other, even if we had managed to recruit to target. We calculated the fragility index, which is the number of currently randomised women who should have been seizure free, to show a 25% decrease in seizures, as postulated in our sample size calculation. Only 36 women should have suffered seizures, compared with the observed number of 48 women, a significant number that should have been reduced. We also calculated the additional number of women needed to show statistical significance for the effect size as observed. Assuming that the observed effect size and SD holds, we estimate that the number of women that would need to be recruited to demonstrate a significant effect of therapeutic drug monitoring and clinical features monitoring on time to first seizure and time to any seizure was 1038 and 1302, respectively.

The risk of seizure deterioration was not significantly different in the non-randomised group with stable serum AED levels and those with a decrease of $\geq 25\%$, reinforcing the lack of benefit of routine drug monitoring. Furthermore, we observed a significant increase in the cord blood levels of lamotrigine and levetiracetam in women whose AED doses were managed based on therapeutic drug monitoring. Given the above findings, in the absence of firm evidence on long-term neurodevelopmental outcomes in infants exposed to AEDs, particularly the newer AEDs such as levetiracetam, caution is required prior to routine dose escalation based on serum AED levels alone.

Our qualitative study findings have led to the following recommendations on care for pregnant women living with epilepsy.

- Pre-conception information: pre-conception counselling interventions need to continue to work towards better identifying, and reaching out to, women who are not accessing this information, and to provide consistent information on whether or not they should start a family.
- Antenatal care and medication management: women's varied positions on the spectrum of seizure types need be more fully recognised by health professionals, as this informs how women understand and manage their condition. It should also be recognised that women's decisions to stop, reduce, maintain or increase their AEDs over the course of their pregnancies are based on a rationale of maternal responsibility towards their babies.
- Postnatal care: ward practices need to facilitate appropriate access for partners and families of women with epilepsy in order to manage their condition following delivery.
- Supporting mothers with epilepsy: women would benefit from more advice and information concerning modifying their caregiving practices (changing nappies on the floor, never bathing babies alone, etc.), as these practices were often not considered fully until after the babies were born.

Recommendations for future research

Given the difficulties in achieving the target sample size, despite recruitment in more than 50 centres, conducting future randomised trials with a large sample size will be challenging. Any such trials will need to take into account the core outcomes needed for minimal reporting to enable meaningful evidence synthesis. The risks of seizure deterioration for various threshold levels of decrease in AEDs need further

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evaluation. A robust risk assessment method, using an individualised prediction model by taking into account mothers' clinical characteristics including type and duration of seizure, type of AED and change in serum AED levels, will help to identify those women who need close monitoring in pregnancy. Importantly, the long-term neurodevelopment of the infants born to mothers in both randomised groups, and any impact on health-care costs, need further evaluation.

In relation to the qualitative research on pregnant women's experiences of managing epilepsy, additional research is needed with women with less controlled and/or more frequent seizures. As the qualitative study was carried out alongside the EMPiRE trial, which included only women who had chosen to have children, there is a risk of bias as those women having children may have better-managed seizures and fewer negative symptoms and side effects associated with their medication. Furthermore, there is a need for a more integrated approach in future research in this area to provide a more comprehensive picture of the clinical and experiential aspects of taking AEDs.

Chapter 6 Conclusion

In pregnant women with epilepsy on AEDs such as lamotrigine, carbamazepine, levetiracetam and phenytoin as mono- or polytherapy, regular monitoring of drug levels to inform dosage of AED does not significantly reduce the risk of seizure deterioration or lower maternal and fetal complications compared with management based on clinical features alone. Infants born to women in the therapeutic drug monitoring group were exposed to higher levels of AEDs than those in the clinical features monitoring arm.

The qualitative study sought to address the dearth of research on women's experiences of pregnancy while managing their epilepsy and, to date, is one of only two studies in this area.[30] Findings suggested that a tension exists between the professional's focus on drug adherence and the patient's experience of doubt, as she must live with the consequences of drug regimens. Furthermore, women's varied positions on the spectrum of seizure types must be more fully recognised, as this informs how they understand and manage their condition. In relation to the trial, qualitative findings on women's rationales for declining the trial highlight that the randomisation process was not acceptable to some women as they felt they could potentially lose control over the management of their medication, which, in turn, could lead to a seizure during pregnancy.

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Acknowledgements

We would like to thank all the principal investigators, co-ordinating midwives, epilepsy specialist nurses, consultant obstetricians and neurologists, co-ordinators and data assistants at each of the recruiting hospitals for their dedication and hard work in promoting the study, recruiting participants and for data entry.

Our thanks to the TSC, chaired by Ben Mol (independent obstetrician), and DMC, chaired by Carl Clarke (independent neurologist), for their constant support throughout the trial.

Acknowledgements also go to the staff at the co-ordinating centre: Women's Health Research Unit of Queen Mary University of London, Anna Placzek (data administrator), Camille Paulsen (administrator), Joyce Kibaru (data assistant), Malika Barakat (data assistant) and Janet Godfrey (administrator). We also thank the Pragmatic Clinical Trials Unit of Queen Mary University of London for their assistance in the development and management of the study database.

We thank Epilepsy Action for their promotion and guidance in developing the study design.

We would also like to acknowledge the National Institute for Health Research Health Technology Assessment programme for their ongoing support and advice during the trial.

Finally, we would like to thank each and every participant who consented to take part in the EMPiRE study.

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Shakila Thangaratinam (Professor of Maternal and Perinatal Health) designed and led the project, provided clinical direction, and prepared and edited the final report.

Nadine Marlin (Statistician) wrote the statistical analysis plan, provided statistical support, performed the statistical analysis of the study and contributed to the final report.

Sian Newton (Trial Co-ordinator) supervised the general management of the study and its data collection, and assisted with the report.

Annalise Weckesser (Qualitative Researcher) ran the qualitative study, developed the qualitative section of the report and provided input towards the report.

Manny Bagary (Lead Neuropsychiatrist) contributed to the design of the trial and provided clinical advice.

Lynette Greenhill (Lead Epilepsy Specialist Nurse) assisted with the design of the trial, and provided advice and support.

Rachel Rikunenko (Trial Co-ordinator) supervised the general management of the study and contributed to the report.

Maria D'Amico (Research Assistant) entered and cleaned data, and edited the report.

Ewelina Rogozińska (Project Co-ordinator) supported the trial and its data collection, and contributed to the final report.

Andrew Kelso (Neurologist) provided clinical input and contributed to the report.

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Kelly Hard (Research and Development Manager) assisted with the design of the trial, and provided advice and support towards the report.

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Angela Pullen (Epilepsy Action Representative) helped draft and review the lay summary of the final report, provided advice and helped promote the study.

Sandra Eldridge (Statistician) delivered statistical supervision, contributed to the analysis plan and the final report.

Alexander Pirie (National Lead in Obstetrics) was involved in conception, design and conduct of the trial, and provided clinical direction.

Elaine Denny (Qualitative Lead) assisted with the development of the study, ran the qualitative study, contributed to the qualitative report and provided input towards the draft.

Doug McCorry (Lead Neurologist) assisted with the development of the study, provided clinical input and support, and contributed to the report.

Khalid S Khan (Professor of Women's Health and Clinical Epidemiology) designed the project, provided overall direction, and contributed to and edited the report.

Data sharing statement

Study data can be obtained from the corresponding author.

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Appendix 1 Amendments to protocol

The trial protocol is available online.[51]

TABLE 17 Amendments to the protocol

What was proposed in original grant application	What was done in the EMPiRE study
1. The original target sample size was 1000 women with epilepsy on AEDs	There were difficulties meeting this target. An extension was requested in order to meet the recruitment target, which was rejected and recruitment stopped at 557
2. Data were collected for a health economic evaluation	It was decided that the analysis of these data will be parked until further funding is available
3. The BSID was being used to assess mental and motor development of the infant at the 6-week postnatal visit	It was agreed by the TSC that the BSID would not collect valuable data at such an early stage in a child's development and was removed from the protocol
4. Serum albumin levels were to be checked on visits 1, 3 and 5	Serum albumin levels are not routinely checked, and committee members felt that the logistics and cost of the test outweighed the research benefits
5. Cord blood was not initially being taken at delivery	Committee members felt strongly that it was important to obtain data on the levels of AED transferred from the mother to baby
6. Suspected non-adherence to AED was not initially being documented	Further clarification of action to be taken regarding suspected non-adherence was necessary. Clinicians of group B[a] non-adherent patients were to be unblinded
7. Participants were sent the patient information sheet 7 days before their booking visit to allow time to consider consenting to the trial	Patients were sent the patient information sheet 24 hours before the booking visit in an attempt to increase recruitment
8. There was no option for clinicians to request additional serum levels to be taken	This was added as an option for circumstances in which there is a clinical suspicion of toxicity or non-adherence
9. The NDDI-E tool was not originally being used	The NDDI-E questionnaire was included as part of baseline data collection
10. Serum AED samples for participants in group B were not frozen until the end of the trial	Freezing blood samples in group B was introduced to mirror existing clinical practice, as many units do not routinely check serum AED levels
11. The QOLIE-31 tool was filled out at each monthly visit	The QOLIE-31 questionnaire was lengthy and only necessary to be conducted at baseline and then once between 32 and 36 weeks' gestation
12. Only clinicians were consenting women in to the trial	Specialist midwives and suitably qualified members of staff at a site were able to consent participants into the trial
13. The original inclusion criteria stated that women who have a confirmed viable pregnancy of < 16 weeks' gestation can be recruited	This was amended to include women who have a confirmed viable pregnancy of < 24 weeks' gestation (23 weeks and 6 days) in order to increase recruitment
14. Exclusion criteria included women who have a history of poor adherence	The exclusion criteria were amended to include women who clearly expressed an intention not to take AEDs in pregnancy or come to the clinic regularly. It allowed clinicians not to recruit someone who had a chaotic follow-up and planned to do that for the rest of the pregnancy

continued

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TABLE 17 Amendments to the protocol (*continued*)

What was proposed in original grant application	What was done in the EMPiRE study
15. Clarification was required for unblinding to serum AED levels	Clinicians and participants will automatically be unblinded if there is an undetectable serum AED level at any time for participants in groups A[b] and C[c]. Clinicians and participants will not be automatically unblinded to undetectable serum AED levels for participants randomised to group B
16. Maternal bloods were to be collected at delivery, and the postnatal visit will be conducted at 6 weeks post delivery	It was clarified that maternal delivery bloods could be collected at any point between labour admission up to discharge. The postnatal visit could be conducted at any point between 6 and 8 weeks post delivery

BSID, Bayley Scales of Infant Development.
a Group B, clinical features monitoring.
b Group A, therapeutic drug monitoring.
c Group C, not randomised.

Appendix 2 Maternal outcomes

TABLE 18 Maternal adverse effects of AED exposure: lamotrigine alone

Outcome	Number of mothers	Mean lamotrigine exposure in mg (SD)		Measure	Effect of increasing exposure (95% CI)
		No outcome	Outcome		
LAEP score	178	N/A	N/A	IRR	1.0 (1.0 to 1.0)
Gestational age at delivery	257	N/A	N/A	MD	0.00 (–0.00 to 0.02)
CS or instrumental delivery	255	273 (153)	287 (156)	OR	1.0 (1.0 to 1.0)
Pre-term labour	249	281 (155)	253 (149)	OR	1.0 (1.0 to 1.0)
Induction of labour	254	273 (151)	301 (165)	OR	1.0 (1.0 to 1.0)
Pre-eclampsia	248	279 (154)	293 (165)	OR	1.0 (1.0 to 1.0)
Gestational diabetes mellitus	248	276 (150)	374 (234)	OR	1.0 (1.0 to 1.0)
Antepartum haemorrhage	187	277 (154)	351 (172)	OR	1.0 (1.0 to 1.0)
Postpartum haemorrhage	254	272 (152)	312 (159)	OR	1.0 (1.0 to 1.0)
Admission to HDU or ICU	249	277 (154)	310 (160)	OR	1.0 (1.0 to 1.0)
Feeding	253			OR	1.0 (1.0 to 1.0)
Breast		264 (132)			
Mixed		300 (177)			
Bottle		309 (186)			

CS, caesarean section; HDU, high-dependency unit; ICU, intensive care unit; IRR, incidence rate ratio; N/A, not applicable; OR, odds ratio.

Note

Clustering of multiple fetuses by mother ignored as a result of convergence issues.

TABLE 19 Mean difference AED exposure by occurrence of maternal adverse events: lamotrigine alone

Adverse events	Number of mothers	MD in lamotrigine exposure (95% CI)
CS or instrumental delivery	255	24.1 (–12.5 to 60.8)
Pre-term labour	256	–11.2 (–85.3 to 62.9)
Induction of labour	254	22.2 (–20.0 to 64.4)
Pre-eclampsia	255	14.8 (–89.4 to 119.0)
Gestational diabetes mellitus	255	50.0 (–46.0 to 146.0)
Antepartum haemorrhage	254	100.9 (–3.8 to 205.6)
Postpartum haemorrhage	254	49.2 (–0.8 to 99.2)
Admission to HDU or ICU	256	31.6 (–49.5 to 112.7)
Feeding	253	
Breast		Reference group
Mixed		33.3 (–25.7 to 92.3)
Bottle		38.8 (–4.6 to 82.1)

CS, caesarean section; HDU, high-dependency unit; ICU, intensive care unit.

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TABLE 20 Maternal adverse effects of AED exposure: levetiracetam alone

Outcome	Number of mothers	Mean levetiracetam exposure in mg (SD)		Measure	Effect of increasing exposure (95% CI)
		No outcome	Outcome		
LAEP score	88	N/A	N/A	IRR	1.0 (1.0 to 1.0)
Gestational age at delivery	126	N/A	N/A	MD	0.0 (0.0 to 0.0)
CS or instrumental delivery	124	1740 (987)	1548 (641)	OR	1.0 (1.0 to 1.0)
Pre-term labour	96	1634 (864)	1888 (639)	OR	1.0 (1.0 to 1.0)
Induction of labour	125	1620 (868)	1694 (834)	OR	1.0 (1.0 to 1.0)
Pre-eclampsia	51	1645 (859)	1825 (459)	OR	1.0 (1.0 to 1.0)
Gestational diabetes mellitus	124	1627 (807)	1471 (611)	OR	1.0 (0.998 to 1.0)
Antepartum haemorrhage	70	1639 (859)	2033 (454)	OR	1.0 (1.0 to 1.0)
Postpartum haemorrhage	127	1684 (890)	1396 (470)	OR	1.0 (1.0 to 1.0)
Admission to HDU or ICU	125	1662 (858)	1314 (715)	OR	1.0 (1.0 to 1.0)
Feeding	125			OR	1.000 (1.0 to 1.0)
Breast		1599 (897)			
Mixed		1928 (1022)			
Bottle		1611 (592)			

CS, caesarean section; HDU, high-dependency unit; ICU, intensive care unit; IRR, incidence rate ratio; N/A, not applicable; OR, odds ratio.

Note

Clustering of multiple fetuses by mother ignored as a result of convergence issues.

TABLE 21 Mean difference AED exposure by occurrence of maternal adverse events: levetiracetam alone

Adverse events	Number of mothers	MD in levetiracetam exposure (95% CI)
CS or instrumental delivery	126	–226.4 (–536.3 to 83.5)
Pre-term labour	127	23.6 (–644.4 to 691.5)
Induction of labour	127	7.7 (–307.4 to 322.8)
Pre-eclampsia	127	358.0 (–823.6 to 1539.5)
Gestational diabetes mellitus	126	–109.5 (–815.6 to 596.6)
Antepartum haemorrhage	127	507.2 (–459.5 to 1473.9)
Postpartum haemorrhage	127	–365.5 (–817.5 to 86.6)
Admission to HDU or ICU	127	–431.7 (–1184.8 to 321.5)
Breastfeeding		
126 (128)	125	Reference group
97 (98)		246.5 (–153.4 to 646.5)
50 (51)		–28.5 (–382.0 to 325.0)

CS, caesarean section; HDU, high-dependency unit; ICU, intensive care unit.

TABLE 22 Maternal adverse effects of AED exposure: carbamazepine alone

Outcome	Number of mothers	Mean carbamazepine exposure in mg (SD)		Measure	Effect of increasing exposure (95% CI)
		No outcome	Outcome		
LAEP score	60	N/A[a]	N/A	IRR	1.0 (1.0 to 1.0)
Gestational age at delivery	86	N/A	N/A	MD	–0.01 (–0.02 to 0.0)
CS or instrumental delivery	86	632 (317)	711 (290)	OR	1.0 (1.0 to 1.0)
Pre-term labour	82	647 (295)	842 (315)	OR	1.0 (1.0 to 1.0)
Induction of labour	82	631 (274)	747 (340)	OR	1.0 (0.1 to 1.0)
Pre-eclampsia	81	676 (305)	604 (303)	OR	1.0 (0.1 to 1.0)
Gestational diabetes mellitus	63	665 (305)	831 (249)	OR	1.0 (1.0 to 1.0)
Antepartum haemorrhage	63	671 (305)	800 (283)	OR	1.0 (0.98 to 1.06)
Postpartum haemorrhage	82	664 (297)	764 (363)	OR	1.0 (1.0 to 1.0)
Admission to HDU or ICU	63	676 (308)	623 (167)	OR	1.0 (0.99 to 1.01)
Feeding	85			OR	1.0 (1.0 to 1.0)
Breast		689 (336)			
Mixed		634 (275)			
Bottle		665 (174)			

CS, caesarean section; HDU, high-dependency unit; ICU, intensive care unit; IRR, incidence rate ratio; N/A, not applicable; OR, odds ratio.
a Not applicable as outcome and exposure variable are continuous.
Note
Clustering of multiple fetuses by mother ignored as a result of convergence issues.

TABLE 23 Mean difference AED exposure by occurrence of maternal adverse events: carbamazepine alone

Adverse events	Number of mothers	MD in carbamazepine exposure (95% CI)
CS or instrumental delivery	86	18.2 (–111.7 to 148.0)
Pre-term labour	86	179.0 (4.3 to 353.8)
Induction of labour	86	76.0 (–52.9 to 204.9)
Pre-eclampsia	85	–46.6 (–273.4 to 180.1)
Gestational diabetes mellitus	86	70.6 (–197.1 to 338.4)
Antepartum haemorrhage	86	254.7 (–152.0 to 661.5)
Postpartum haemorrhage	86	85.8 (–111.4 to 283.0)
Admission to HDU or ICU	86	16.4 (–316.4 to 349.2)
Feeding	85	
Breast		Reference group
Mixed		–80.6 (–276.7 to 115.6)
Bottle		–2.2 (–168.4 to 163.9)

CS, caesarean section; HDU, high-dependency unit; ICU, intensive care unit.

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TABLE 24 Maternal adverse effects of AED exposure: lamotrigine and levetiracetam

Outcome	Number of mothers	Measure	Mean lamotrigine exposure in mg (SD)		Effect of increasing exposure (95% CI)	Mean levetiracetam exposure in mg (SD)		Effect of increasing exposure (95% CI)
			No outcome	Outcome		No outcome	Outcome	
LAEP score	22	IRR	N/A	N/A	1.0 (1.000 to 1.001)	N/A	N/A	1.0 (1.0 to 1.0)
Gestational age at delivery	36	MD	N/A	N/A	–0.01 (–0.050 to 0.030)	N/A	N/A	0.0 (–0.01 to 0.00)
CS or instrumental delivery	35	OR	376 (169)	451 (177)	1.0 (1.000 to 1.025)	1867 (913)	2060 (1028)	1.0 (1.0 to 1.0)
Pre-term labour	35	OR	421 (175)	424 (190)	1.0 (0.995 to 1.008)	1880 (873)	2508 (1364)	1.0 (1.0 to 1.0)
Induction of labour	35	OR	420 (205)	423 (129)	0.9991.0 (0.99 to 1.0	2053 (1137)	1889 (720)	1.0 (1.0 to 1.0)
Pre-eclampsia	23	OR	401 (169)	518 (34)	Perfect prediction	2038 (961)	1743 (1316)	Perfect prediction
Gestational diabetes mellitus	–	OR	410 (167)	450	Perfect prediction	1941 (891)	4462	Perfect prediction
Antepartum haemorrhage	–	OR	422 (178)	400	Perfect prediction	2013 (976)	1000	Perfect prediction
Postpartum haemorrhage	24	OR	387 (161)	566 (169)	1.0 (0.99 to 1.0)	1967 (963)	2060 (1106)	1.0 (1.0 to 1.0)
Admission to HDU or ICU	–	OR	423 (180)	400 (0)	Perfect prediction	2028 (986)	1250 (354)	Perfect prediction
Feeding	36	OR						
Breast			446 (186)		0.99 (0.99 to 1.0)	2180 (969)		1.0 (1.0 to 1.0)
Mixed			523			2000		
Bottle			404 (174)			1882 (1008)		

CS, caesarean section; HDU, high-dependency unit; ICU, intensive care unit; IRR, incidence rate ratio; N/A, not applicable; OR, odds ratio.

Note

Clustering of multiple fetuses by mother ignored as a result of convergence issues.

TABLE 25 Mean difference AED exposure by occurrence of maternal adverse events: lamotrigine and levetiracetam

Adverse events	Number of mothers	MD in lamotrigine exposure (95% CI)	MD in levetiracetam exposure (95% CI)
CS or instrumental delivery	36	87.3 (–46.8 to 221.5)	30.5 (–771.0 to 832.0)
Pre-term labour	36	15.3 (–146.4 to 177.0)	557.0 (–355.7 to 1469.7)
Induction of labour	36	–23.1 (–173.1 to 126.9)	87.0 (–783.1 to 957.2)
Pre-eclampsia	35	124.0 (–84.2 to 332.3)	–5.1 (–1337.0 to 1326.8)
Gestational diabetes mellitus	35	–89.4 (–460.1 to 281.4)	2205.7 (56.8 to 4354.7)
Antepartum haemorrhage	36	79.1 (–340.6 to 498.8)	–919.0 (–3331.4 to 1493.4)
Postpartum haemorrhage	36	142.8 (–11.6 to 297.2)	–253.6 (–1198.7 to 691.5)
Admission to HDU or ICU	36	48.8 (–247.2 to 344.9)	–593.1 (–2296.9 to 1110.8)
Feeding	36		
Breast		Reference group	Reference group
Mixed		–29.7 (–428.8 to 369.3)	–332.227 (–2680.7 to 2016.2)
Bottle		–74.0 (–209.9 to 61.9)	–250.6 (–1050.4 to 549.3)

CS, caesarean section; HDU, high-dependency unit; ICU, intensive care unit.

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Appendix 3 Fetal outcomes

TABLE 26 Fetal adverse effects of AED exposure: lamotrigine alone

Outcome	Number of mothers (number of babies)	Mean lamotrigine exposure in mg (SD)		Measure	Effect of increasing exposure (95% CI)
		No outcome	Outcome		
Cord blood levels, lamotrigine (mg/l)	186 (188)	N/A	N/A	MD	0.01 (0.01 to 0.01)
Major congenital malformations	247 (254)	276 (156)	302 (116)	OR[a]	1.0 (1.0 to 1.01)
Baby's admission to neonatal unit	254 (247)	279 (153)	273 (162)	OR	1.0 (1.0 to 1.0)
Apgar score at 1 minute	247 (252)	N/A	N/A	MD	-1×10^{-4} (–0.001 to 0.001)
Apgar score at 5 minutes	249 (254)	N/A	N/A	MD	3×10^{-4} (–0.001 to 0.001)
Birthweight (kg)	254 (261)	N/A	N/A	MD	4×10^{-4} (-2×10^{-4} to 0.001)
Birthweight < 10th centile	254 (261)	279 (152)	268 (170)	OR	1.0 (1.0 to 1.0)
Head circumference (cm)	202 (206)	N/A	N/A	MD	-1×10^{-4} (–0.001 to 0.002)
Cord pH A	103 (104)	N/A	N/A	MD	-2×10^{-4} (-3×10^{-4} to 7×10^{-4})
Cord pH V	109 (110)	N/A	N/A	MD[a]	-2×10^{-4} (-3×10^{-4} to -3×10^{-5})

A, arterial; N/A, not applicable; OR, odds ratio; V, venous.
a Clustering of multiple fetuses by mother ignored as a result of convergence issues.

TABLE 27 Mean difference AED exposure by occurrence of fetal adverse events: lamotrigine alone

Adverse events	Number of mothers (number of babies)	MD in lamotrigine exposure (95% CI)
Major congenital malformations	247 (254)	39.0 (–31.6 to 109.6)
Baby's admission to neonatal unit	254 (247)	4.2 (–53.5 to 61.8)
Apgar score at 1 minute (< 7[a])	247 (252)	9.0 (–73.5 to 91.5)
Apgar score at 5 minutes (< 7[a])	249 (254)	90.9 (–40.5 to 222.3)
Birthweight < 10th centile	254 (261)	–33.4 (–94.5 to 27.7)
Cord pH A (< 7[a])	103 (104)	–144.9 (–356.6 to 66.8)
Cord pH V (< 7[a])	109 (110)	–77.2 (–388.1 to 233.7)

A, arterial; V, venous.
a Number of babies with Apgar score of < 7.

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TABLE 28 Fetal adverse effects of AED exposure: levetiracetam alone

Outcome	Number of mothers (number of babies)	Mean levetiracetam exposure in mg (SD)		Measure	Effect of increasing exposure (95% CI)
		No outcome	Outcome		
Cord blood levels, levetiracetam (mg/l)	94 (95)	N/A	N/A	MD[a]	**0.01 (0.01 to 0.01)**
Major congenital malformations	126 (128)	1646 (858)	1859 (593)	OR	1.0 (1.0 to 1.01)
Baby's admission to neonatal unit	124 (126)	1626 (789)	2063 (1415)	OR	1.0 (1.0,1.0)
Apgar score at 1 minute	123 (125)	N/A	N/A	MD[a]	-8×10^{-6} (-3×10^{-4} to 3×10^{-4})
Apgar score at 5 minutes	123(125)	N/A	N/A	MD[a]	-4×10^{-5} (-2×10^{-4} to 1×10^{-4})
Birthweight (kg)	126 (128)	N/A	N/A	MD	6×10^{-5} (-3×10^{-5} to 2×10^{-4})
Birthweight < 10th centile	126 (128)	1609 (804)	1928 (1041)	OR	1.0 (1.0 to 1.0)
Head circumference (cm)	97 (98)	N/A	N/A	MD[a]	3×10^{-4} (-7×10^{-5} to 0.001)
Cord pH A	50 (51)	N/A	N/A	MD[a]	–0.005 (–0.01 to 0.00)
Cord pH V	59 (61)	N/A	N/A	MD	–0.003 (–0.01 to 0.00)

A, arterial; N/A, not applicable; OR, odds ratio; V, venous.
a Clustering of multiple fetuses by mother ignored as a result of convergence issues.
Note
Bold text denotes statistically significant results at the 5% level.

TABLE 29 Mean difference AED exposure by occurrence of fetal adverse events: levetiracetam alone

Adverse events	Number of mothers (number of babies)	MD in levetiracetam exposure (95% CI)
Major congenital malformations	126 (128)	149.3 (–572.1 to 870.6)
Baby's admission to neonatal unit	124 (126)	362.2 (–206.5 to 930.9)
Apgar score at 1 minute (< 7[a])	123 (125)	–47.5 (–638.2 to 543.2)
Apgar score at 5 minutes (< 7[a])	123 (125)	Perfect prediction
Birthweight centile < 10th centile	126 (128)	225.4 (–216.0 to 666.8)
Cord pH A (< 7[a])	50 (51)	Perfect prediction
Cord pH V (< 7[a])	59 (61)	Perfect prediction

A, arterial; V, venous.
a Number of babies with Apgar score of < 7.

TABLE 30 Fetal adverse effects of AED exposure: carbamazepine alone

Outcome	Number of mothers (number of babies)	Mean carbamazepine exposure in mg (SD)		Measure	Effect of increasing exposure (95% CI)
		No outcome	Outcome		
Cord blood levels, carbamazepine (mg/l)	62 (64)	N/A	N/A	MD[a]	**0.00 (0.00 to 0.00)**
Major congenital malformations	85 (88)	670 (285)	688 (398)	OR	1.0 (1.0 to 1.0)
Baby's admission to neonatal unit	85 (88)	677 (290)	644 (358)	OR	1.0 (0.99 to 1.0)
Apgar score at 1 minute	84 (87)	N/A	N/A	MD	0.00 (0.00 to 0.00)
Apgar score at 5 minutes	84 (87)	N/A	N/A	MD[a]	-9×10^{-5} (–0.001 to 0.001)
Birthweight (kg)	85 (88)	N/A	N/A	MD	0.00 (0.00 to 0.00)
Birthweight centile < 10th centile	85 (88)	640 (299)	777 (281)	OR	1.0 (1.0 to 1.0)
Head circumference (cm)	63 (66)	N/A	N/A	MD	0.00 (0.00 to 0.00)
Cord pH A	35 (36)	N/A	N/A	MD	1×10^{-5} (-1×10^{-4} to 1×10^{-4})
Cord pH V	40 (40)	N/A	N/A	MD[a]	1×10^{-5} (-1×10^{-4} to 1×10^{-4})

A, arterial; N/A, not applicable; OR, odds ratio; V, venous.
a Clustering of multiple fetuses by mother ignored as a result of convergence issues.

TABLE 31 Mean difference AED exposure by occurence of fetal adverse events: carbamazepine alone

Adverse events	Number of mothers (number of babies)	MD in carbamazepine exposure (95% CI)
Major congenital malformations	85 (88)	–14.1 (–198.9 to 170.8)
Baby's admission to neonatal unit	85 (88)	–58.8 (–231.4 to 113.7)
Apgar score at 1 minute (< 7[a])	84 (87)	–110.7 (–308.7 to 87.4)
Apgar score at 5 minutes (< 7[a])	84 (87)	7.7 (–284.7 to 300.2)
Birthweight < 10th centile	85 (88)	132.1 (–5.7 to 269.9)
Cord pH A (< 7[a])	35 (36)	Perfect prediction
Cord pH V (< 7[a])	40 (40)	32.8 (–624.2 to 689.9)

A, arterial; V, venous.
a Number of babies with Apgar score of < 7.

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TABLE 32 Fetal adverse effects of AED exposure: lamotrigine and levetiracetam

Outcome	Number of mothers (number of babies)	Measure	Mean lamotrigine exposure in mg (SD)			Mean levetiracetam exposure in mg (SD)		
			No outcome	Outcome	Effect of increasing exposure (95% CI)	No outcome	Outcome	Effect of increasing exposure (95% CI)
Cord blood levels, lamotrigine (mg/l)	27	MD	N/A	N/A	**0.009 (0.004 to 0.013)**	N/A	N/A	-2×10^{-4} (–0.001 to 0.001)
Cord blood levels, levetiracetam (mg/l)					0.008 (–0.026 to 0.041)			**0.008 (0.002 to 0.013)**
Major congenital malformations	22 (24)	OR	429 (179)	391 (13)	Perfect prediction	2011 (989)	1750 (354)	Perfect prediction
Baby's admission to neonatal unit	36 (38)	OR	421 (171)	440 (188)	1.005 (0.989 to 1.021)	1841 (767)	2297 (1244)	1.002 (0.998 to 1.006)
Apgar score at 1 minute	35 (37)	MD[a]	N/A	N/A	3×10^{-4} (–0.004 to 0.005)	N/A	N/A	0.000 (0.000 to 0.001)
Apgar score at 5 minutes	35 (37)	MD[a]	N/A	N/A	0.001 (–0.002 to 0.003)	N/A	N/A	0.000 (0.000 to 0.001)
Birthweight (kg)	35 (37)	MD	N/A	N/A	–0.001 (–0.002 to 0.000)	N/A	N/A	0.000 (0.000 to 0.000)
Birthweight < 10th centile	15 (17)	OR	420 (185)	473 (115)	Perfect prediction	1898 (947)	2218 (685)	Perfect prediction
Head circumference (cm)	27 (28)	MD	N/A	N/A	–0.001 (–0.005 to 0.002)	N/A	N/A	0.001 (-2×10^{-4} to 0.001)
Cord pH A	13 (14)	MD[a]	N/A	N/A	2×10^{-4} (-3×10^{-4} to 0.001)	N/A	N/A	6×10^{-5} (-1×10^{-4} to 2×10^{-4})
Cord pH V	14 (16)	MD	N/A	N/A	2×10^{-4} (5×10^{-5} to 3×10^{-4})	N/A	N/A	-3×10^{-5} (-9×10^{-5} to 2×10^{-5})

A, arterial; N/A, not applicable; OR, odds ratio; V, venous.

a Clustering of multiple fetuses by mother ignored as a result of convergence issues.

Note

Bold text denotes statistically significant results at the 5% level.

TABLE 33 Mean difference AED exposure by occurrence of fetal adverse events: lamotrigine and levetiracetam

Adverse events	Number of mothers (number of babies)	MD in lamotrigine exposure (95% CI)	MD in levetiracetam exposure (95% CI)
Major congenital malformations	22 (24)	–11.5 (–288.6 to 265.7)	–317.8 (–1920.0 to 1284.6)
Baby's admission to neonatal unit	36 (38)	46.2 (–87.5 to 179.9)	522.5 (–233.5 to 1278.4)
Apgar score at 1 minute (< 7[a])	35 (37)	–42.1 (–239.8 to 155.5)	964.7 (–53.5 to 1982.9)
Apgar score at 5 minutes (< 7[a])	35 (37)	–128.2 (–551.8 to 295.4)	951.9 (–1351.1 to 3254.9)
Birthweight < 10th centile	15 (17)	161.3 (–15.4 to 338.0)	289.6 (–729.1 to 1308.2)
Cord pH A (< 7[a])	13 (14)	Perfect prediction	Perfect prediction
Cord pH V (< 7[a])	14 (16)	Perfect prediction	Perfect prediction

A, arterial; V, venous.
a Number of babies with Apgar score of < 7.

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Appendix 4 Qualitative interview guide

Antenatal Interview

Interviewee Name: _____ **Date:** _____

Prior to interview: Told Others of Interview Local & Time ___, Extra Batteries ___, Pen & Pad ___, Epilepsy Nurse/ Support Contact Numbers___

Pre Interview Checklist	X
Understands qualitative study	
Received and read the PIS	
Answer participant's questions	
Consented to take part obtained	
If not participating in trial: Interview consent signed	
Consented to record	

Field Notes (Details of where interviewed, who present, etc.)

Demographic Info

Age: _____

# of children: _____

Stage in pregnancy: _____

Due Date: _____

Ethnicity (self-identified): _____

Religion: _____

Occupation: _____

Marital Status: _____

Years had epilepsy: _____

Type of Epilepsy (self-defined):

_____

Mailing Address: _____

_____

Email: _____

Trial Number: _____

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RECORDER ON

1. Managing Epilepsy Outside of Pregnancy

What would you like to call your condition? Is this how you usually refer to it?

Take me back to when you first had __[reflect language back]__. Please tell me the story of when this first occurred.

- Prompts: What happened, who was there…

- **What do you call these events (i.e. seizures/episodes/fits)?**

- **Please describe what these [participant's term] are like.**

- How did you receive your diagnosis? When did your receive it?

- How did you feel about the diagnosis?

How does ____[participant's term]___ fit into your day to day life? Tell me about what your normal day-to-day life is like.

- Who have you told? Who do you talk to about this?

- Who do you get support from? How do they support you?

- Does [participant's term] interfere with your day to day life? How?

What drugs you have taken in the past? And now?

Epilepsy is often thought of as a stigmatising condition. How do you feel about that? Is that true for you?

2. Preconception Experience

**First-time pregnancy:*

Before becoming pregnant- thinking about your __[epilepsy/participant's term]___ -how did you feel about pregnancy?

- Did you have any concerns/hopes?

- What did you think about your medication and becoming pregnant?

**Those with previous pregnancies:*

Tell me about what your past pregnancy/ies where like.

- Did this influence how you planned for this pregnancy?

- Did you have any concerns/hopes for this second/third/fourth… pregnancy?

Tell me about your labour experience

* *All participants*

How did you learn you were pregnant?

- How did you feel?

- How did others (partners, family, etc.) feel?

How did you find information about pregnancy while having [epilepsy/ participant's term] ?

- Prompts: From where? Who?

- What did you think of this information? Was it helpful?

3. Experience of Pregnancy

How do you feel about being pregnant and having epilepsy?

-Has the way you manage your [participant's term] changed? How? Can you give an example?

-How have you changed your life in relation to [participant's term] since becoming pregnant?

As you know you are receiving additional ante-natal care because of your epilepsy, which means that you are in a category of high risk. Has anyone mentioned that to you? How do you feel about being categorised as high risk?

Why did (or didn't*) you decide to take part in this trial?

*If opted out- can I ask why you chose not to participate?

-How do you feel about the: drug regime, blood tests, hospital visits, and monitoring by the clinic?

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4. Weighing Up Risks vs. Benefits

How do you weigh up the risks vs the benefits of having baby while living with [epilepsy /participants' term]?

Cover the following areas through conversation:

- Risks of [epilepsy/participant's term] on *your baby?*
- Risks to *yourself*?

- Benefits of [epilepsy/participant's term] on *your baby*?
- Benefits to *yourself*?

- Risks of epilepsy management/medication on *your baby*?
- Risks to *yourself*?

- Benefits of epilepsy management/medication on *your baby*?
- Benefits to *yourself*?

- Risks of seizures on *your baby*?
- Risks to *yourself*?

If participant sees seizures as positive:

- How do you weigh up the benefits of seizures on *your baby*?
- And the benefits to *yourself*?

Who do you talk to about managing your [epilepsy/participant's terms] during your pregnancy?

What influences how you make decisions regarding managing epilepsy during your pregnancy?

- Who influences these decisions?

- Who supports you? How do they support you?

5. Tell me about your experience (of care/at the clinic)

- How have your interactions with the doctors/nurses been? Expand/tell me more/give an example
- Your concerns about (what stated in previous questions), have you raised them with nurses/doctors? How did you feel about the information/advice they gave you?
- Do you feel you get all your questions answered?
- Do you have enough time with nurses/doctors?

6. Concerns and Hopes for the Future

- What are your main concerns about the rest of your pregnancy?
- What are your hopes for the rest of the pregnancy?

- Do you have concerns about the labour?
- What are hopes for the labour?

- After the labour, and your baby is born, what are your hopes for your baby?
- Do you have any concerns for your baby?

- Do you have any concerns for yourself after the baby arrives?
- What are your hopes for yourself after the baby arrives?

7. Concluding Questions

Is there anything else we didn't discuss that you would like to talk about?

Do you have questions for me?

RECORDER OFF

Post Interview Checklist	X
Ask participant if could contact us if she has a seizure during pregnancy	
Give or mail voucher	
Type field notes and reflections	
Transcribe demographic details in reporter's notebook	
Save recorded interview in computer and hard drive	
Destroy this form and any written notes	

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Postnatal Interview

Interviewee Name: _____ **Date:** _____

Prior to interview: Told Others of Interview Local & Time ___, Extra Batteries ___, Pen & Pad ___, Epilepsy Nurse/ Support Contact Numbers___,

REVIEW PREVIOUS INTERVIEW(S)___

Make list of previous responses about management of epilepsy and pregnancy, and risks vs. benefits ___

Note participant's term for epilepsy ___

Pre Interview Checklist	X
Answer participant's questions	
Consent for continued participation obtained (verbal)	
Consented to record	

Field Notes (Details of where interviewed, who present, etc.)

RECORDER ON

1. **Tell me how you have been since we last spoke**
   -How was the rest of the pregnancy
   -Tell me about the labour
   -How have you and the baby been since the labour

2. **Thinking back, how do you feel about taking your medication while being pregnant?**
   [refer to their response in previous interview(s)]

3. **Is there anything you feel could have been done differently/ better?**

4. [If have NOT yet talked about high risk pregnancies before] **As you know you received additional ante-natal care because of your epilepsy, which means that**

your pregnancy was categorised as high risk. Had anyone mentioned that to you? How do you feel about your pregnancy being categorised as high risk?

[If have ALREADY talked about high risk pregnancies before] **We talked about your being in a high risk category before. In hindsight, how do you feel about your pregnancy being categorised as high risk?**

5. **Are you managing your (epilepsy/participants' own term) any differently now? If so, how? If not** [probe more]

    - Medication/dosage

6. **Thinking back to our conversation about the risks and benefits for your baby –** *[remind them of their previous answers]* - **how do you feel now about those concerns after your baby has been born?**

7. **Does your (epilepsy/participant's own term) influence how you care for your child? How? Are you taking extra precautions (in regards to below)?**
    - Can you an example/tell me about X
    - Feeding Child (Breast, bottle, and where)
    - Bathing Child
    - Rest, Sleep for baby/you, and sleeping arrangements?
    - Going outside with your baby?
    - **Supports from friends, family?**
    - **Supports from health visitors/midwives?**
        - Visits in home?
        - Questions answered?
        - Enough time?
        - Quality of information?

8. **If you did not have (epilepsy/participant's own term) do you think the way you care for your baby day to day would be different?**
    - **If yes, how?**
    - **If no, why not?**

9. **Tell me about your experience of being in the Trial**
    - Can you give an example/ tell me more about X

10. **Tell me about your experience of care during the pregnancy**
    - had questions answered
    - enough time with doctors/nurses
    - quality of information, responses, diagnosis
    - Can you give me an example/tell me more about X

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11. Concluding Questions:

Is there anything else we didn't discuss that you would like to talk about?

Do you have questions for me?

RECORDER OFF

Post Interview Checklist	X
Check if received voucher, or verify is coming	
Type field notes and reflections	
Save recorded interview in computer and hard drive	
Destroy this form and any written notes	

Appendix 5 Definition of the primary outcome

TABLE 34 Definition of the primary outcome

Outcome	Definition
Time from randomisation to first TCS	• Time between a 25% reduction in serum AED levels and the first TCS. A TCS (or grand mal seizure) is a common generalised seizure, meaning that it affects both sides of the brain. It involves strong muscular contractions, convulsions and a loss of consciousness
Time from randomisation to any other seizure	• Time between a 25% reduction in serum AED levels and the first seizure that is not a TCS. Seizures are categorised as generalised (affecting the entire brain) or focal (affecting one area of the brain) • Other generalised seizures are absences (or petit mal seizures), which involve a brief loss of consciousness, and myoclonic seizures, which typically involve muscle jerks and can occur in clusters • Focal seizures include complex partial seizures, in which consciousness is affected and involuntary movements (automatisms), such as lip smacking, occur. During a simple partial seizure, the person is aware and alert, and symptoms vary depending on the area of the brain affected

TCS, tonic–clonic seizure.

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Appendix 6 List of core outcomes for studies on pregnant women with epilepsy (Delphi)

TABLE 35 Core outcomes for studies on pregnant women with epilepsy (Delphi)

Outcomes		
Neurological	**Fetal and neonatal**	**Obstetric**
• AED toxicity[a] • Compliance with AED[a] • Drowning • Maternal death • Postnatal depression • Seizure control (post partum and in pregnancy) • QoL • Status epilepticus • Sudden unexpected death in epilepsy	• Admission to neonatal intensive care unit • Autism spectrum disorder • Anthropometric measurements including birthweight • Fetal anticonvulsant syndrome[a] • Congenital abnormalities (major and minor) • Neonatal haemorrhagic disease[a] • Neurodevelopment[a] • Neonatal withdrawal symptoms[a] • Neonatal clinical complications[b] • Stillbirth	• Admission to high-dependency or intensive care unit • Breastfeeding rate[a] • Hypertensive disorder (pre-eclampsia, eclampsia) • Pregnancy outcome (live birth rate, ectopic pregnancy, miscarriage, termination of pregnancy) • Mode of delivery • Pre-term birth

a Outcomes applicable only in studies on pregnant women on antiepileptic agents.
b Acute respiratory distress syndrome, anaemia hypoglycaemia, hyperglycaemia, hypocalcaemia, hypotonia, feeding problems, sedation syndrome, icterus/convulsions, cephalhaematoma and Apgar scores.
Some content from Al Wattar *et al.*[52]

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Appendix 7 List of collaborators

The EMPiRE trial collaborative network:

- Dr Shanika Samarasekera – Queen Elizabeth Hospital, Birmingham
- Professor Rajat Gupta – Birmingham Children's Hospital, Birmingham
- Dr Naghme Adab – University Hospital of Coventry and Warwickshire
- Professor Ismail Khaled – Keele University Medical School and University of North Staffordshire
- Mr Lee Middleton – Birmingham University, Birmingham
- Miss Manjo Doug – Birmingham Women's NHS Foundation Trust, Birmingham
- Professor Tracy Baker – Birmingham
- Dr Salwa El-Taher – Arrowe Park Hospital, Wirral
- Dr Catharina Schram – Royal Blackburn Hospital, Lancashire; Burnley General Hospital, Lancashire
- Dr Virginia Beckett – Bradford Royal Infirmary, Bradford
- Dr Jim Morrow – Royal Victoria Hospital, Belfast
- Mr Alexander Pirie – Birmingham Women's Hospital, Birmingham
- Dr Neil Shah – Birmingham City Hospital, Birmingham
- Dr Fadi Alfhaily – Colchester Hospital, Colchester
- Ms Sadia Malick – University Hospitals Coventry and Warwickshire, Coventry
- Dr Mark Johnson – Chelsea and Westminster Hospital, London
- Miss Sasha Rajendran – The Royal Derby Hospital, Derby
- Dr Alastair Campbell – Edinburgh Royal Infirmary, Edinburgh
- Dr John O'Dwyer – Frimley Park Hospital, London
- Miss Maggie Armstrong – Glan Clwyd Hospital, Rhyl
- Dr Charlotte Lawthorn – Royal Gwent Hospital, Newport
- Dr Janet Brennand – Southern General Hospital, Glasgow
- Dr Isaac Babarinsa – Gloucester Royal Hospital, Gloucestershire
- Dr Avideah Nejad – Royal Hampshire County Hospital, Hampshire
- Dr Gary Dennis – Royal Hallamshire Hospital, Sheffield
- Dr Jacqueline Tay – Leeds General Infirmary, Leeds
- Dr Manjiri Khare – University Hospitals of Leicester, Leicester
- Dr Feroza Dawood – Liverpool Women's Hospital, Liverpool
- Dr Charlotte Lawthorn – Neville Hall Hospital, Abergavenny
- Dr Tadala Saukila – University Hospital of Durham, Newcastle upon Tyne
- Mr Wesley McCullough – Northampton General Hospital, Northamptonshire
- Dr Alpa Shah – Newham Hospital, London
- Dr Fidelma O'Mahoney – University Hospital of North Staffordshire, Staffordshire
- Miss Abha Govind – North Middlesex University Hospital, London
- Dr Oier Aeka and Dr Lucy Mackillop – John Radcliffe Hospital, Oxford
- Dr Karen Brackley – Princess Anne Hospital, Southampton
- Dr Mukta Bhattacharya – Queen Alexandra Hospital, Portsmouth
- Dr Leye Thompson – Queen's Hospital, Romford
- Dr Sophia Stone – St Richard's Hospital, Chichester
- Dr Philippa Marsden – Royal Victoria Infirmary, Newcastle upon Tyne
- Dr Rehan Khan – The Royal London Hospital, London
- Miss Heather Brown – Royal Sussex County Hospital, Brighton
- Mr Narayanaswamy Raman – Southend Hospital, Westcliff on Sea
- Dr Hanah Cock – St George's Hospital, London
- Dr Robert Powell – Singleton Hospital, Swansea
- Dr Teresa Kelly – St Mary's Hospital, Manchester
- Dr Aarti Ullal – Sunderland Royal Hospital, Sunderland

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- Mr Phil Tittensor – Stafford General Hospital, Stafford
- Dr Adam Gornall – Royal Shrewsbury Hospital, Shrewsbury
- Dr Aylur Rajasri – Royal Cornwall Hospital (Treliske), Truro
- Professor Catherine Nelson-Piercy – St Thomas' Hospital, London
- Dr Khalid Hamandi – University Hospital of Wales, Cardiff
- Dr Rita Arya – Warrington Hospital, Warrington
- Dr Lakshmi Thirumalaikumar – Worcestershire Royal Hospital, Worcester
- Dr Sophia Stone – Worthing Hospital, Western Sussex
- Dr Sujatha Thamban – Whipps Cross Hospital, London.

Appendix 8 Recruitment at each site

TABLE 36 Breakdown of recruitment by site

Site	Trial group, *n*			
	Randomised		Non-randomised (*N* = 294)	Total (*N* = 557), *n*
	TDM (*N* = 130)	CFM (*N* = 133)		
Arrowe Park Hospital	0	1	1	2
Royal Blackburn Hospital	1	4	6	11
Bradford General Hospital	2	2	2	6
Royal Victoria Hospital	2	5	5	12
Birmingham Women's Hospital	12	10	27	49
Burnley General Hospital	0	3	5	8
Birmingham City Hospital	5	0	3	8
Colchester General Hospital	3	2	6	11
University Hospital Coventry	3	0	4	7
Chelsea & Westminster Hospital	3	3	4	10
Royal Derby Hospital	2	3	4	9
Royal Edinburgh Infirmary	1	3	1	5
Frimley Park Hospital	3	0	5	8
Glan Clwyd Hospital	5	5	7	17
Royal Gwent Hospital	2	1	5	8
Southern General Hospital	2	5	6	13
Gloucester Royal Hospital	1	0	2	3
Royal Hampshire County Hospital	1	2	5	8
Jessop Hospital	5	3	14	22
Leeds General Infirmary	3	2	6	11
Leicester Royal Infirmary	1	1	7	9
Liverpool Women's Hospital	3	4	15	22
Nevill Hall Hospital	1	0	2	3
University Hospital of North Durham	1	2	5	8
Northampton General Hospital	0	2	1	3
Newham University Hospital	1	1	4	6
North Staffordshire Hospital	4	1	6	11
North Middlesex University Hospital	0	1	1	2
John Radcliffe Hospital	2	3	6	11
Southampton General Hospital	3	1	7	11

continued

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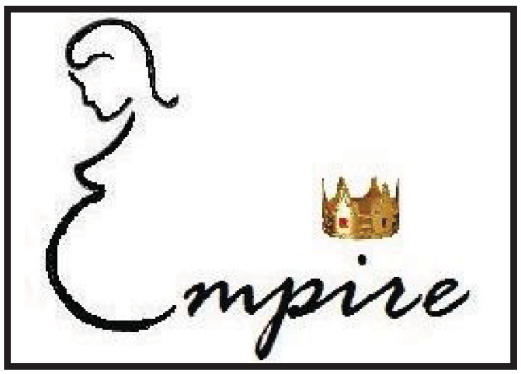
TABLE 36 Breakdown of recruitment by site (*continued*)

Site	Trial group, *n*			
	Randomised		Non-randomised (*N* = 294)	Total (*N* = 557), *n*
	TDM (*N* = 130)	CFM (*N* = 133)		
Queen Alexandra Hospital	2	0	3	5
Queen's Hospital	7	7	13	27
St Richard's Hospital	3	6	9	18
Royal Victoria Infirmary	7	5	10	22
Royal London Hospital	2	1	5	8
Royal Sussex County Hospital	1	0	5	6
Southend University Hospital	2	6	2	10
St George's Hospital	4	3	10	17
Singleton Hospital	5	4	7	16
Salford Royal	1	2	5	8
Sunderland Royal Hospital	6	3	2	11
Stafford Hospital	7	6	4	17
Royal Shrewsbury Hospital	3	1	5	9
Royal Cornwall Hospital	2	2	2	6
St Thomas' Hospital	1	7	19	27
University Hospital of Wales	0	2	5	7
Warrington Hospital	0	2	4	6
Worcestershire Royal Hospital	4	3	6	13
Worthing Hospital	1	1	4	6
Whipps Cross University Hospital	0	2	2	4

CFM, clinical features monitoring; TDM, therapeutic drug monitoring.

Appendix 9 Case report form

Baseline booklet



BASELINE BOOKLET

Patient UTIN: _ _/_ _ _

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BASELINE BOOKLET	Visit checklist 1	Participant UTIN	Visit date
		_ _/_ _ _	DD /MMM /YYYY

CHECKLIST (Completed Y/N)		ACTION
Have you advised the trial office that the participant has been recruited to EMPIRE by faxing Recruitment form: Parts 1 & 2?	**Yes** ☐	File completed **Recruitment Form: parts 1 & 2**
	No ☐	Send **Recruitment Form: parts 1 & 2** AND EMPIRE Trial blood request form to the trial office. Proceed according to SOP no. 3 Blood collection and processing
Has a blood sample been taken?	**Yes** ☐	Centrifuge and package sample according to SOP no. 3 Blood collection and processing
	No ☐	Please take blood sample and package according to SOP no. 3 Blood collection and processing Or Document reason why blood sample was not taken ***Please state here:***
Have you provided the participant with the EMPIRE diary?	**Yes** ☐	Explain how diary is to be completed.
	No ☐	Please provide participant with diary and explain how it is to be completed. Or Document reason why diary not given ***Please state here:***
Have you completed Baseline Booklet?	**Yes** ☐	File **Baseline Booklet** in participant's CRF file.
	No ☐	Complete **Baseline Booklet** and file in participant's CRF file.
Has the participant completed: **Patient's questionnaire (EQ-5d, LAEP& cost questionnaire)**	**Yes** ☐	Return completed **Patient's questionnaire** to participant's CRF file.
	No ☐	Ask participant to complete **Patient's questionnaire** and file in participant's CRF file. OR Document reason why not completed. ***Please state here:***

To be continued on the next page

BASELINE BOOKLET	Visit checklist 2	Participant UTIN	Visit date
		__ __/__ __ __	DD /MMM /YYYY

CHECKLIST (Completed Y/N)		ACTION
Has the participant completed: **QOLIE 31 questionnaire?**	**Yes** ☐	Return completed **QOLIE 31 questionnaire** to participant's CRF file.
	No ☐	Ask participant to complete **QOLIE 31 questionnaire** and file in participant's CRF file. OR Document reason why not completed. ***Please state here:***
Has the participant completed: **NDDI-E screening tool?**	**Yes** ☐	Return completed **NDDI-E** to participant's CRF file. Score above 15 may imply existence of depression. If the case, please refer accordingly to your usual clinical practice.
	No ☐	Ask participant to complete **NDDI-E screening tool** and file in participant's CRF file. **OR** Document reason why not completed. ***Please state here:***
Have you completed Purple Alert and Adverse Events Forms?	**Yes** ☐	File is in participant's CRF file.
	No ☐	Complete if necessary and file in participant's CRF file.

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BASELINE BOOKLET	Recruitment form Part 1	Participant UTIN	Visit date
		_ _/_ _ _	DD /MMM /YYYY

IMPORTANT: Part 1 & 2 of this form MUST be completed and sent to the Trial Co-ordinator along with the EMPIRE blood request form on the day of the participant's recruitment

Please, state the date when the patient consent was obtained	DD /MMM /YYYY

PRE-TRIAL SERUM AED LEVEL (PRE-PREGNANCY OR EARLY PREGNANCY)

As the treating clinician you have the choice of setting a pre-pregnancy serum AED level (PPSL) OR the Early Pregnancy serum AED level (taken in pregnancy prior to trial baseline visit) (EPSL) as the 'target' level. If a pre-pregnancy level is to be used it should be taken within the last 12 months. You should be confident that when this level was taken the participant was adherent to treatment, on the same current daily dosage and ideally the time interval between the oral dosage and serum level will be similar to those taken throughout the pregnancy.

PRE-PREGNANCY SERUM AED LEVEL (PPSL)	
As the treating clinician are you confident that:	
The participant's serum level has been taken pre-pregnancy and recorded in the last 12 months?	**Yes** ☐ **No** ☐
You know the timing of the serum level and the last dose taken?	**Yes** ☐ **No** ☐
Do you think the serum level of AED in pre-pregnancy takes into account the time of the day of intake?	**Yes** ☐ **No** ☐
If you have answered yes to all the above are you happy for the pre-pregnancy serum AED level to be the target level for the trial?	**Yes** ☐ **No** ☐
If yes, please set pre-pregnancy serum AED level as the target AED level for the trial.	
EARLY PREGNANCY SERUM AED LEVEL (EPSL) (TAKEN IN PREGNANCY PRIOR TO TRIAL BASELINE VISIT)	
As the treating clinician are you confident that:	
The participant's serum level has been taken in this pregnancy?	**Yes** ☐ **No** ☐
You know the timing of the serum level and the last dose taken?	**Yes** ☐ **No** ☐
Do you think the serum level of AED in this pregnancy takes into account the time of the day of intake?	**Yes** ☐ **No** ☐
If you have answered yes to all the above are you happy for the pre-trial serum AED level to be the target level for the trial?	**Yes** ☐ **No** ☐
If yes, please set pregnancy serum AED level as the target AED level for the trial. **Do that *ONLY* if pre-pregnancy level is not set as a target.**	

BASELINE BOOKLET	Recruitment form Part 2	Participant UTIN	Visit date
		__ __/__ __ __	__ /MMM /YYYY

Please present all available data regarding pre-trial AED serum levels i.e. pre-pregnancy AED serum levels (PPSL), early pregnancy serum levels (EPSL) or both.

Current AED Please use Brand name, if prescribed	Total daily dose (mg)	AED serum level known	SERUM LEVEL Value	SERUM LEVEL Unit	Date AED level taken	Use as the EMPIRE serum target level
carbamazepine (generic) Yes ☐ No ☐		PPSL ☐		µmol/l ☐ mg/l ☐	__ /MMM /YYYY	Yes ☐ No ☐
Tegretol (brand) Yes ☐ No ☐		EPSL ☐		µmol/l ☐ mg/l ☐	__ /MMM /YYYY	Yes ☐ No ☐
Tegretol Retard (brand) Yes ☐ No ☐		Neither ☐				
lamotrigine (generic) Yes ☐ No ☐		PPSL ☐		µmol/l ☐ mg/l ☐	__ /MMM /YYYY	Yes ☐ No ☐
		EPSL ☐		µmol/l ☐ mg/l ☐	__ /MMM /YYYY	Yes ☐ No ☐
Lamictal (brand) Yes ☐ No ☐		Neither ☐				
levetiracetam (generic) Yes ☐ No ☐		PPSL ☐		µmol/l ☐ mg/l ☐	__ /MMM /YYYY	Yes ☐ No ☐
		EPSL ☐		µmol/l ☐ mg/l ☐	__ /MMM /YYYY	Yes ☐ No ☐
Keppra (brand) Yes ☐ No ☐		Neither ☐				
phenytoin (generic) Yes ☐ No ☐		PPSL ☐		µmol/l ☐ mg/l ☐	__ /MMM /YYYY	Yes ☐ No ☐
		EPSL ☐		µmol/l ☐ mg/l ☐	__ /MMM /YYYY	Yes ☐ No ☐
Epanutin (brand) Yes ☐ No ☐		Neither ☐				

Gestational age	_____weeks _____days
Did the participant experience seizures (any type) during the 3 months prior to her pregnancy?	**Yes** ☐ **No** ☐

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BASELINE BOOKLET	Baseline form AED Medication	Participant UTIN	Visit date
		_ _/_ _ _	DD / MMM / YYYY

AED MEDICATION

This part is to be used to document all dose changes for **all AED medication** taken 6 months prior to the start of the trial up until this visit.

Medication	Total daily dose (mg)	Start date	Ongoing?	End date
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY

BASELINE BOOKLET	Baseline form Non-AED Medication	Participant UTIN	Visit date
		__/___	DD / MMM / YYYY

NON-AED MEDICATION

This part is to be used to document all dose changes for **all** **non AED medication** taken 6 months prior to the start of the trial up until the final post natal visit.

Medication	Total daily dose (mg)	Start date	Ongoing?	End date
Folic Acid		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
Vitamin K		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
Methyldopa		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
Nifedipine		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
Insulin		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
Metformin		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
Labetelol		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
Ferrous sulphate		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
Aspirin		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
If any other medication is being used, please specify medication name and fill in following gaps. ***If not applicable please cross the section.***				
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY

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BASELINE BOOKLET	Baseline Form Surgical & Obstetric History	Participant UTIN	Visit date
		__ __/__ __ __	__ /___ /____

SURGICAL HISTORY

Has the participant had any intracranial surgery prior to the study visit?	**Yes** ☐ **No** ☐
If yes, please specify	
Date	__ /___ /____

VAGAL NERVE STIMULATION (VNS)

Does the patient have a VNS device fitted?	**Yes** ☐ **No** ☐	**If yes, current status of the VNS device**	**On** ☐ **Off** ☐

GRAVIDA & PARITY

Gravida (Number of pregnancies including this one)		**Parity** (Number of previous births at 24 weeks or more gestation)	

PREVIOUS PREGNANCY COMPLICATIONS

Has the participant had any terminations or miscarriages? *If yes, please specify below:*			**Yes** ☐ **No** ☐
Total number of terminations			
Total number of miscarriages			
Number of 1st trimester miscarriages		**Number of 2nd trimester miscarriages**	

Previous maternal history					
Pre-eclampsia	**Yes** ☐ **No** ☐	Eclampsia	**Yes** ☐ **No** ☐	Gestational diabetes	**Yes** ☐ **No** ☐
Antepartum haemorrhage	**Yes** ☐ **No** ☐	Abruption	**Yes** ☐ **No** ☐	Caesarean section	**Yes** ☐ **No** ☐
Postpartum haemorrhage	**Yes** ☐ **No** ☐	Infection	**Yes** ☐ **No** ☐	Other	**Yes** ☐ **No** ☐
***If Other**, please specify*					
Admission to hospital due to seizures in previous pregnancies				**Yes** ☐ **No** ☐	

BASELINE BOOKLET	Baseline Form Medical History (excluding epilepsy)	Participant UTIN	Visit date
		__ __/__ __ __	__ /___ /____

MEDICAL HISTORY

Is there a history of:		Patient	Family history
1. Congenital abnormalities		Yes ☐ No ☐	Yes ☐ No ☐
2. Learning difficulties		Yes ☐ No ☐	Yes ☐ No ☐
3. Diabetes		Yes ☐ No ☐	Yes ☐ No ☐
4. Chronic Hypertension		Yes ☐ No ☐	Yes ☐ No ☐
5. Renal disease		Yes ☐ No ☐	Yes ☐ No ☐
6. Immunological problems		Yes ☐ No ☐	Yes ☐ No ☐
If yes, please specify:	a) Systemic Lupus	Yes ☐ No ☐	Yes ☐ No ☐
	b) Erythematosis	Yes ☐ No ☐	Yes ☐ No ☐
	c) Rheumatoid arthritis	Yes ☐ No ☐	Yes ☐ No ☐
	d) If other, please specify here		
7. Cardiac disease		Yes ☐ No ☐	Yes ☐ No ☐
	If yes, please specify here		
8. Haematological disorders		Yes ☐ No ☐	Yes ☐ No ☐
If yes, please specify:	a) Deep vein thrombosis	Yes ☐ No ☐	Yes ☐ No ☐
	b) Pulmonary embolism	Yes ☐ No ☐	Yes ☐ No ☐
	c) Thrombocytopenia	Yes ☐ No ☐	Yes ☐ No ☐
	d) If other, please specify here		
9. HIV		Yes ☐ No ☐	Yes ☐ No ☐
10. Tuberculosis		Yes ☐ No ☐	Yes ☐ No ☐

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11. Any genetically inherited disorders *If yes, please specify here*	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
12. Mental illness	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
If yes, please specify: a) Majo r depression	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
b) Puerperal psychosis	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
c) Bipolar disorder	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
d) Schizophrenia	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐
e) If other, please specify here		
13. Any other *If yes, please specify here*	**Yes** ☐ **No** ☐	**Yes** ☐ **No** ☐

BASELINE BOOKLET	Baseline Form Epilepsy History	Participant UTIN	Visit date
		_ _/_ _ _	DD /MMM /YYYY

DIAGNOSIS OF EPILEPSY

Age at first seizure (excluding febrile)	years	Date of first seizure (excluding febrile)	DD /MMM /YYYY

AETIOLOGY OF EPILEPSY

Idiopathic, assumed genetic	☐		
Structural *(if yes, please specify)*	☐	**Trauma** ☐ **Space occupying lesions** ☐ **Vascular malformation** ☐	**Stroke** ☐ **SLE** ☐ **Other** *(if yes please specify below)* ☐
Cryptogenic	☐		
Infection *(if yes, please specify)*	☐	**Encephalitis** ☐	**HIV** ☐
Metabolic *(if yes, please specify)*	☐	**Alcohol** ☐	**Drug** ☐

EPILEPSY SYNDROME

Syndrome		Please tick one
Partial Epilepsy	Symptomatic or cryptogenic partial epilepsy	☐
	Temporal lobe	☐
	Frontal lobe	☐
	Parietal lobe	☐
	Occipital lobe	☐
	Localisation unknown	☐
Generalised	Juvenile myoclonic epilepsy	☐
	Tonic clonic seizures on wakening	☐
	Childhood absence epilepsy	☐
	Juvenile absence epilepsy	☐
Unclassified Epilepsy/Other syndromic diagnosis		☐

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BASELINE BOOKLET	Baseline Form Seizure types	Participant UTIN	Visit date
		_ _/_ _ _	DD /MMM /YYYY

SEIZURE CLASSIFICATION & FREQUENCY

Seizure description (s) Has the participant ever experienced any of the following:		Yes/No	Number of seizures in the 3 months prior to pregnancy (if exact number not known, please give best estimate)	Number of seizures since becoming pregnant (if exact number not known, please give best estimate)
Generalized	Tonic clonic *(including secondary generalized seizures)*	**Yes** ☐ **No** ☐		
	Absence	**Yes** ☐ **No** ☐		
	Myoclonus	**Yes** ☐ **No** ☐		
Partial	Simple	**Yes** ☐ **No** ☐		
	Complex	**Yes** ☐ **No** ☐		
Unclassified/Other		**Yes** ☐ **No** ☐		

CLUSTERS

Has the patient had a seizure cluster?	Yes ☐ No ☐	Date of last seizure cluster	DD /MMM /YYYY

BASELINE BOOKLET	Baseline Form EEG/MRI	Participant UTIN	Visit date
		__ __/__ __ __	__ /__ /__

EEG INTERPRETATION (IF AVAILABLE)

Has an EEG been performed at any time?	**Yes** ☐ **No** ☐	**Date**	DD /MMM /YYYY
Result known *If **yes,** please specify outcome below:*	**Yes** ☐ **No** ☐		
Is EEG normal?	**Yes** ☐ **No** ☐		
If abnormal, is it clinically significant?	**Yes** ☐ **No** ☐		
If clinically significant please specify — **Focal epileptiform discharges** ☐		*If **yes**, please specify:*	
Generalised epileptiform discharges ☐		*If **yes**, please specify:*	
Other ☐		*If **yes**, please specify:*	

MRI/CT INTERPRETATION (IF AVAILABLE)

Has an MRI been performed at any time?	**Yes** ☐ **No** ☐	**Date**	DD / MMM / YYYY
Result known	**Yes** ☐ **No** ☐	*If **yes,** please specify outcome:*	
Has the MRI demonstrated aetiology of epilepsy? *If yes, please specify below*	**Yes** ☐ **No** ☐		
Tumour	**Yes** ☐ **No** ☐	**Vascular malformation**	**Yes** ☐ **No** ☐
Previous trauma	**Yes** ☐ **No** ☐	**Hippocampal sclerosis**	**Yes** ☐ **No** ☐
Previous stroke	**Yes** ☐ **No** ☐	**Cortical dysplasia**	**Yes** ☐ **No** ☐
Other *(if yes please specify)*	**Yes** ☐ **No** ☐		
Has a CT been performed?	**Yes** ☐ **No** ☐	**Date**	DD / MMM / YYYY
Result known	**Yes** ☐ **No** ☐	*If **yes,** please specify outcome:*	
Has the CT demonstrated aetiology of epilepsy? *If yes, please specify:*	**Yes** ☐ **No** ☐		
Tumour	**Yes** ☐ **No** ☐	**Previous stroke**	**Yes** ☐ **No** ☐
Previous trauma	**Yes** ☐ **No** ☐	**Vascular malformation**	**Yes** ☐ **No** ☐
Other, *if yes please specify*	**Yes** ☐ **No** ☐		

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BASELINE BOOKLET	Baseline Form Demographics Part 1	Participant UTIN	Visit date
		_ _/_ _ _	DD /MMM /YYYY

DEMOGRAPHICS

MOTHER'S ETHNIC GROUP

Please tick only one

White		Black or Black British	
British	☐	African	☐
Irish	☐	Caribbean	☐
White other	☐	Black other	☐

Asian or Asian British		Mixed		Other ethnic group	
Bangladeshi	☐	Mixed – White/Black African	☐	Other ethnic group	☐
Indian	☐	Mixed – White/Black Caribbean	☐		
Pakistani	☐	Mixed – White/Asian	☐	Not given	☐
Chinese	☐	Mixed – White/Chinese	☐		
Asian other	☐	Mixed other	☐		

HEIGHT AND WEIGHT

Height	cm	Weight	kg

PATIENT'S AGE

Years		Months	

BASELINE BOOKLET	Baseline Form Demographics Part 2	Participant UTIN	Visit date
		__ __/__ __ __	DD /MMM /YYYY

EMPLOYMENT & DRIVING STATUS

Employed – Full-time ☐		**Holds a valid driving licence**	**Yes** ☐ **No** ☐
Employed – Part-time ☐			
Self – employed ☐		**Medically fit to drive**	**Yes** ☐ **No** ☐
Unemployed ☐			

EDUCATIONAL DETAILS

Highest qualification	Degree Level ☐
	A Level ☐
	GCSE Level ☐
	Below GCSE Level ☐
School leaving age	_____ yrs

NICOTINE & ALCOHOL CONSUMPTION DURING PREGNANCY

Smoker	☐	***If yes, specify*** **number of cigarettes per day**		
Ex-smoker	☐	***If yes, specify*** **how long ago patient stopped smoking**	0 – 3 months ☐	3+ months ☐
Non-smoker	☐			

Average number of alcohol units <u>per week</u>	

Examples

Units	Example
1 unit	Half pint of ordinary strength beer, lager, or cider (3-4% alcohol by volume) or a small pub measure (25 ml) of spirits (40% alcohol by volume)
2 units	Medium glass of 12.5% wine (175ml) or can of 4.5% beer (440ml)
3 units	Large glass of 12.5% wine (250ml) or pint of 6% cider

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BASELINE BOOKLET	Baseline Form Previous children	Participant UTIN	Visit date
		__ __/__ __ __	DD /MMM /YYYY

CHILDREN

Please use the following sheets to document information about all of the participant's previous births/children. Please begin with the most recent birth/child. One sheet should be used per child.
If not applicable, please cross all irrelevant sections.

Child number		**Gender**	**Male** ☐ **Female** ☐	**DOB**	DD /MMM /YYYY
Gestational age at delivery		**wks**		**Birth weight**	**kg**
Neonatal death		**Yes** ☐ **No** ☐		**Still birth**	**Yes** ☐ **No** ☐
Delivery mode	**Spontaneous Vaginal** ☐	**Forceps** ☐	**Ventouse** ☐	**Caesarean section** ☐	
AED Exposure *If **yes,** please **specify AEDs** taken when pregnant with this child:*			**Yes** ☐ **No** ☐		
lamotrigine	**Yes** ☐ **No** ☐		**levetiracetam**	**Yes** ☐ **No** ☐	
carbamazepine	**Yes** ☐ **No** ☐		**sodium valproate**	**Yes** ☐ **No** ☐	
phenytoin	**Yes** ☐ **No** ☐		**Other,** *if yes please specify*	**Yes** ☐ **No** ☐	
Congenital malformations *(if **yes**, please specify below)*			**Yes** ☐ **No** ☐		
Spina bifida	**Yes** ☐ **No** ☐		**Hydrocephalus**	**Yes** ☐ **No** ☐	
Diaphragmatic hernia	**Yes** ☐ **No** ☐		**Anencephaly**	**Yes** ☐ **No** ☐	
Cleft lip	**Yes** ☐ **No** ☐		**Congenital heart disease**	**Yes** ☐ **No** ☐	
Cleft palate	**Yes** ☐ **No** ☐		**Tumours**	**Yes** ☐ **No** ☐	
Gastroschisis	**Yes** ☐ **No** ☐		**Limb abnormalities**	**Yes** ☐ **No** ☐	
Duodenal atresia	**Yes** ☐ **No** ☐		**External genital abnormalities**	**Yes** ☐ **No** ☐	
Congenital Cystic Adenomatoid Malformation	**Yes** ☐ **No** ☐		**Other,** *if yes please specify*	**Yes** ☐ **No** ☐	
Epilepsy in childhood				**Yes** ☐ **No** ☐	
Regular follow-up for neuro-developmental concerns				**Yes** ☐ **No** ☐	
Statement of special educational needs?				**Yes** ☐ **No** ☐	
ADHD **Attention deficit hyperactivity disorder**	**Yes** ☐ **No** ☐	**Aspergers syndrome**	**Yes** ☐ **No** ☐	**Autism**	**Yes** ☐ **No** ☐

BASELINE BOOKLET	Baseline Form Previous children	Participant UTIN	Visit date
		__ __/__ __ __	__ /__MMM__ /__YYYY__

CHILDREN

Please use the following sheets to document information about all of the participant's previous births/children. Please begin with the most recent birth/child. One sheet should be used per child.
If not applicable, please cross all irrelevant sections.

Child number		**Gender**	**Male** ☐ **Female** ☐	**DOB**	__ /__MMM__ /__YYYY__
Gestational age at delivery		**wks**		**Birth weight**	**kg**
Neonatal death *(below 28 days)*		**Yes** ☐ **No** ☐		**Still birth**	**Yes** ☐ **No** ☐
Delivery mode	**Spontaneous Vaginal** ☐	**Forceps** ☐	**Ventouse** ☐	**Caesarean section** ☐	
AED Exposure *If **yes,** please **specify AEDs** taken when pregnant with this child:*			**Yes** ☐ **No** ☐		
lamotrigine	**Yes** ☐ **No** ☐		**levetiracetam**	**Yes** ☐ **No** ☐	
carbamazepine	**Yes** ☐ **No** ☐		**sodium valproate**	**Yes** ☐ **No** ☐	
phenytoin	**Yes** ☐ **No** ☐		**Other,** *if yes please specify*	**Yes** ☐ **No** ☐	
Congenital malformations *(if **yes**, please specify below)*			**Yes** ☐ **No** ☐		
Spina bifida	**Yes** ☐ **No** ☐		**Hydrocephalus**	**Yes** ☐ **No** ☐	
Diaphragmatic hernia	**Yes** ☐ **No** ☐		**Anencephaly**	**Yes** ☐ **No** ☐	
Cleft lip	**Yes** ☐ **No** ☐		**Congenital heart disease**	**Yes** ☐ **No** ☐	
Cleft palate	**Yes** ☐ **No** ☐		**Tumours**	**Yes** ☐ **No** ☐	
Gastroschisis	**Yes** ☐ **No** ☐		**Limb abnormalities**	**Yes** ☐ **No** ☐	
Duodenal atresia	**Yes** ☐ **No** ☐		**External genital abnormalities**	**Yes** ☐ **No** ☐	
Congenital Cystic Adenomatoid Malformation	**Yes** ☐ **No** ☐		**Other,** *if yes please specify*	**Yes** ☐ **No** ☐	
Epilepsy in childhood				**Yes** ☐ **No** ☐	
Regular follow-up for neuro-developmental concerns				**Yes** ☐ **No** ☐	
Statement of special educational needs?				**Yes** ☐ **No** ☐	
ADHD **Attention deficit hyperactivity disorder**	**Yes** ☐ **No** ☐	**Aspergers syndrome**	**Yes** ☐ **No** ☐	**Autism**	**Yes** ☐ **No** ☐

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BASELINE BOOKLET	Baseline Form Previous children	Participant UTIN	Visit date
		__ __/__ __ __	DD /MMM /YYYY

CHILDREN

Please use the following sheets to document information about all of the participant's previous births/children. Please begin with the most recent birth/child. One sheet should be used per child.
If not applicable, please cross all irrelevant sections.

Child number		**Gender**	**Male** ☐ **Female** ☐	**DOB**	DD /MMM /YYYY
Gestational age at delivery		**wks**		**Birth weight**	**kg**
Neonatal death *(below 28 days)*		**Yes** ☐ **No** ☐		**Still birth**	**Yes** ☐ **No** ☐
Delivery mode	**Spontaneous Vaginal** ☐	**Forceps** ☐	**Ventouse** ☐	**Caesarean section** ☐	
AED Exposure *If **yes,** please **specify AEDs** taken when pregnant with this child:*			**Yes** ☐ **No** ☐		
lamotrigine	**Yes** ☐ **No** ☐		**levetiracetam**	**Yes** ☐ **No** ☐	
carbamazepine	**Yes** ☐ **No** ☐		**sodium valproate**	**Yes** ☐ **No** ☐	
phenytoin	**Yes** ☐ **No** ☐		**Other,** *if yes please specify*	**Yes** ☐ **No** ☐	
Congenital malformations *(if **yes**, please specify below)*			**Yes** ☐ **No** ☐		
Spina bifida	**Yes** ☐ **No** ☐		**Hydrocephalus**	**Yes** ☐ **No** ☐	
Diaphragmatic hernia	**Yes** ☐ **No** ☐		**Anencephaly**	**Yes** ☐ **No** ☐	
Cleft lip	**Yes** ☐ **No** ☐		**Congenital heart disease**	**Yes** ☐ **No** ☐	
Cleft palate	**Yes** ☐ **No** ☐		**Tumours**	**Yes** ☐ **No** ☐	
Gastroschisis	**Yes** ☐ **No** ☐		**Limb abnormalities**	**Yes** ☐ **No** ☐	
Duodenal atresia	**Yes** ☐ **No** ☐		**External genital abnormalities**	**Yes** ☐ **No** ☐	
Congenital Cystic Adenomatoid Malformation	**Yes** ☐ **No** ☐		**Other,** *if yes please specify*	**Yes** ☐ **No** ☐	
Epilepsy in childhood				**Yes** ☐ **No** ☐	
Regular follow-up for neuro-developmental concerns				**Yes** ☐ **No** ☐	
Statement of special educational needs?				**Yes** ☐ **No** ☐	
ADHD Attention deficit hyperactivity disorder	**Yes** ☐ **No** ☐	**Aspergers syndrome**	**Yes** ☐ **No** ☐	**Autism**	**Yes** ☐ **No** ☐

BASELINE BOOKLET	Baseline Form Previous children	Participant UTIN	Visit date
		__ __/__ __ __	__ /__MMM__ /__YYYY__

CHILDREN

Please use the following sheets to document information about all of the participant's previous births/children. Please begin with the most recent birth/child. One sheet should be used per child.
If not applicable, please cross all irrelevant sections.

Child number		**Gender**	**Male** ☐ **Female** ☐	**DOB**	__ /__MMM__ /__YYYY__
Gestational age at delivery		**wks**		**Birth weight**	**kg**
Neonatal death *(below 28 days)*		**Yes** ☐ **No** ☐		**Still birth**	**Yes** ☐ **No** ☐
Delivery mode	**Spontaneous Vaginal** ☐	**Forceps** ☐	**Ventouse** ☐	**Caesarean section** ☐	
AED Exposure *If **yes,** please **specify AEDs** taken when pregnant with this child:*			**Yes** ☐ **No** ☐		
lamotrigine	**Yes** ☐ **No** ☐		**levetiracetam**	**Yes** ☐ **No** ☐	
carbamazepine	**Yes** ☐ **No** ☐		**sodium valproate**	**Yes** ☐ **No** ☐	
phenytoin	**Yes** ☐ **No** ☐		**Other,** *if yes please specify*	**Yes** ☐ **No** ☐	
Congenital malformations *(if **yes**, please specify below)*			**Yes** ☐ **No** ☐		
Spina bifida	**Yes** ☐ **No** ☐		**Hydrocephalus**	**Yes** ☐ **No** ☐	
Diaphragmatic hernia	**Yes** ☐ **No** ☐		**Anencephaly**	**Yes** ☐ **No** ☐	
Cleft lip	**Yes** ☐ **No** ☐		**Congenital heart disease**	**Yes** ☐ **No** ☐	
Cleft palate	**Yes** ☐ **No** ☐		**Tumours**	**Yes** ☐ **No** ☐	
Gastroschisis	**Yes** ☐ **No** ☐		**Limb abnormalities**	**Yes** ☐ **No** ☐	
Duodenal atresia	**Yes** ☐ **No** ☐		**External genital abnormalities**	**Yes** ☐ **No** ☐	
Congenital Cystic Adenomatoid Malformation	**Yes** ☐ **No** ☐		**Other,** *if yes please specify*	**Yes** ☐ **No** ☐	
Epilepsy in childhood				**Yes** ☐ **No** ☐	
Regular follow-up for neuro-developmental concerns				**Yes** ☐ **No** ☐	
Statement of special educational needs?				**Yes** ☐ **No** ☐	
ADHD **Attention deficit hyperactivity disorder**	**Yes** ☐ **No** ☐	**Aspergers syndrome**	**Yes** ☐ **No** ☐	**Autism**	**Yes** ☐ **No** ☐

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BASELINE BOOKLET	Baseline Form Previous children	Participant UTIN	Visit date
		__ __/__ __ __	__ /MMM /YYYY

CHILDREN

Please use the following sheets to document information about all of the participant's previous births/children. Please begin with the most recent birth/child. One sheet should be used per child.
If not applicable, please cross all irrelevant sections.

Child number		**Gender**	**Male** ☐ **Female** ☐	**DOB**	DD /MMM /YYYY
Gestational age at delivery		**wks**		**Birth weight**	**kg**
Neonatal death *(below 28 days)*		**Yes** ☐ **No** ☐		**Still birth**	**Yes** ☐ **No** ☐
Delivery mode	**Spontaneous Vaginal** ☐	**Forceps** ☐	**Ventouse** ☐	**Caesarean section** ☐	
AED Exposure *If **yes**, please **specify AEDs** taken when pregnant with this child:*			**Yes** ☐ **No** ☐		
lamotrigine	**Yes** ☐ **No** ☐		**levetiracetam**	**Yes** ☐ **No** ☐	
carbamazepine	**Yes** ☐ **No** ☐		**sodium valproate**	**Yes** ☐ **No** ☐	
phenytoin	**Yes** ☐ **No** ☐		**Other,** *if yes please specify*	**Yes** ☐ **No** ☐	
Congenital malformations *(if **yes**, please specify below)*			**Yes** ☐ **No** ☐		
Spina bifida	**Yes** ☐ **No** ☐		**Hydrocephalus**	**Yes** ☐ **No** ☐	
Diaphragmatic hernia	**Yes** ☐ **No** ☐		**Anencephaly**	**Yes** ☐ **No** ☐	
Cleft lip	**Yes** ☐ **No** ☐		**Congenital heart disease**	**Yes** ☐ **No** ☐	
Cleft palate	**Yes** ☐ **No** ☐		**Tumours**	**Yes** ☐ **No** ☐	
Gastroschisis	**Yes** ☐ **No** ☐		**Limb abnormalities**	**Yes** ☐ **No** ☐	
Duodenal atresia	**Yes** ☐ **No** ☐		**External genital abnormalities**	**Yes** ☐ **No** ☐	
Congenital Cystic Adenomatoid Malformation	**Yes** ☐ **No** ☐		**Other,** *if yes please specify*	**Yes** ☐ **No** ☐	
Epilepsy in childhood				**Yes** ☐ **No** ☐	
Regular follow-up for neuro-developmental concerns				**Yes** ☐ **No** ☐	
Statement of special educational needs?				**Yes** ☐ **No** ☐	
ADHD **Attention deficit hyperactivity disorder**	**Yes** ☐ **No** ☐	**Aspergers syndrome**	**Yes** ☐ **No** ☐	**Autism**	**Yes** ☐ **No** ☐

Neurological Disorders Depression Inventory for Epilepsy

PATIENT'S QUESTIONAIRE	Baseline visit NDDI-E SCREENING TOOL	Participant UTIN	Visit date
		_ _/_ _ _	DD /MMM /YYYY

EPILEPSY FOUNDATION NEUROLOGICAL DISORDER DEPRESSION INVENTORY FOR EPILEPSY (NDDI-E) SCREENING TOOL

For each item listed below please circle the answer that best describes you (the mother) within the last 2 weeks, including today. If a particular feelings occurred **'always'** or **'often'** circle **4**. If it occurred sometimes circle 3 and so on. Please be sure to answer every item.

	Always or often	Sometimes	Rarely	Never
1. Everything is a struggle	4	3	2	1
2. Nothing I do is right	4	3	2	1
3. Feel guilty	4	3	2	1
4. I'd be better off dead	4	3	2	1
5. Frustrated	4	3	2	1
6. Difficulty finding pleasure	4	3	2	1

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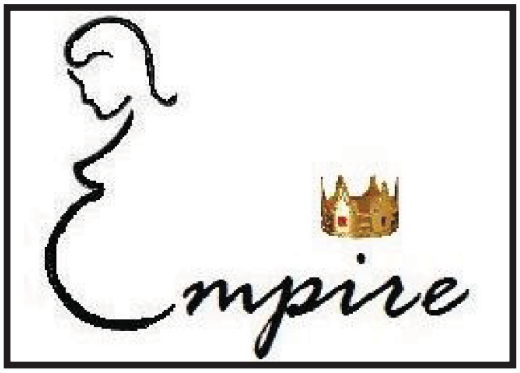
Patient questionnaire



PATIENT'S QUESTIONNAIRE
Patient UTIN: __ __/__ __ __

Please note that the analogous scale was not used.

Health Questionnaire

English version for the UK

(Validated for Ireland)

Sample

UK (English) © 1990 EuroQol Group EQ-5D™ is a trade mark of the EuroQol Group

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities *(e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain / Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety / Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

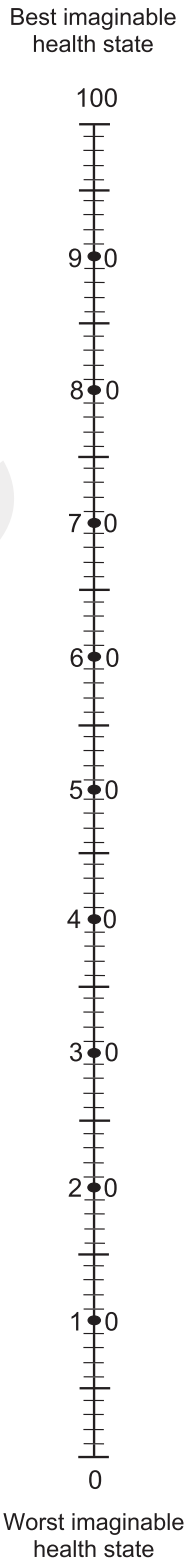
I am extremely anxious or depressed ❑

Sample

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



Sample

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PATIENT'S QUESTIONNAIRE	Cost questionnaire Part 1	Participant UTIN	Visit date
		_ _/_ _ _	DD /MMM /YYYY

QUESTIONNAIRE FOR MEASURING COSTS TO PREGNANT MOTHERS WITH EPILEPSY ON ANTIEPILEPTIC MEDICATION

The aim of the questionnaire:

Health care programmes that treat conditions affect a large number of people. However, very little is known about the hidden costs of these treatments to the health service and to individuals taking part. An estimation of the costs would be incomplete if we did not consider the cost to the patients when attending for treatment. By doing this we can find out if the service we provide is valuable for each individual. The information we get from this questionnaire will help us to find out this valuable information, and will be part of the EMPIRE study.

What you need to do:

We would appreciate it if you would take time to fill in this short questionnaire. Please answer every question. We are interested in this particular visit for your pregnancy. If you are not sure or cannot remember the exact details, please give the best answer you can. You do not have to put your name on the questionnaire and therefore the information you provide is anonymous.

For all visits after the first one

If your travel cost arrangements have not changed since you last filled in the questionnaire, please tick **HERE.** ☐

If they have changed, please can you complete the questionnaire below.

Thank you for your participation in the EMPIRE study, your time and interest are very much appreciated

Thinking about your most recent visit to the hospital clinic:

1. What would have been your **main** activity if you had not attended the clinic?

Paid employment ☐
Looking after relatives ☐
Leisure activities ☐
Housework ☐
Studying at college ☐
Other ☐ *Please specify*_____

PATIENT'S QUESTIONNAIRE	Cost questionnaire Part 2	Participant UTIN	Visit date
		__ __/__ __ __	__ /MMM /YYYY

If you are in paid employment, please answer question 2, if not go to question 3.

2. What arrangements did you make to take time off work? *(Please tick one box)*

Paid absence from work ☐

Unpaid absence from work ☐

Will make the time up ☐

Came to clinic outside work time ☐

Took holiday ☐

Other arrangements ☐ *Please specify*_____

3. How long did it take you to travel to the clinic?

_____ hours _____minutes

4. Approximately what distance did you have to travel to get to the clinic (one-way)?

_____miles

5.a) How did you travel to the clinic? Please tick the main forms of transport.

Walking ☐
Private car ☐
Public transport - bus ☐
Public transport - train ☐
Taxi ☐
Other ☐ *Please specify* _____

b) If you travelled by **private car**, were you given a lift by someone else?

Yes ☐ No ☐

c) If you travelled by **private car**, how much was paid in car park fees?

£____p____

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PATIENT'S QUESTIONNAIRE	Cost questionnaire Part 3	Participant UTIN	Visit date
		__ __/__ __ __	__ /__MMM__ /__YYYY__

d) If you travelled by **public transport (bus or train)**, what was the cost of the one-way fare? If you were given a return fare, simply halve it. Put zero if you did not travel by public transport at all or you did not pay a fare.

£____p____

e) If you travelled by **taxi** what was the cos t of the (one-way) fare? Pu t ze ro if you did not travel by taxi at all or you did not pay a fare.

£____p____

6. Did anyone accompany you to the clinic

and wait for you while you received your care ? Yes ☐ No ☐

If yes, did they take time off work ? Yes ☐ No ☐

7. If you have other dependants,

Did you pay someone to look after them?

Yes ☐ No ☐ Not Applicable ☐

If yes, how much did it cost? £____ p_____

or

Did someone take time off work to look after them? Yes ☐ No ☐

8. How long did you spend waiting at the clinic before your appointment?

_____ hours _____minutes

If you have any comments about your costs for attending the clinic or anything else about this study please write them below.

_____

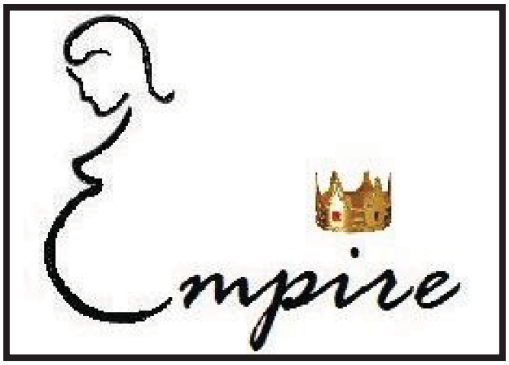
_____

_____

_____

Thank you for taking the time to complete this questionnaire.

Quality Of Life In Epilepsy – 31-item questionnaire



QUALITY OF LIFE IN EPILEPSY QOLIE 31
(Version 1.0 UK)

Patient UTIN: __ __/__ __ __

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PATIENT'S QUESTIONNAIRE	QOLIE 31 Version 1.0 UK Part 1	Participant UTIN	Visit date
		_ _/_ _ _	DD /MMM /YYYY

QUALITY OF LIFE IN EPILEPSY QOLIE – 31 VERSION 1.0

INSTRUCTIONS

The QOLIE-31 is a survey of health related quality of life for adults (18 years or older) with epilepsy. This questionnaire should be completed only by the person who has epilepsy (not a relative or a friend) because no one else knows how YOU feel.

There are 31 questions about your health and daily activities. Answer every question by circling the appropriate number (1, 2, 3....). If you are unsure about how to answer a question, please give the best answer you can and write a comment or explanation on the side of the page. These notes maybe useful if you discuss the QOLIE-31 with your doctor. Completing the QOLIE-31 before and after treatment changes may help you and your doctor understand how the changes have affected your life.

1. Overall, how would you rate your quality of life?

(Please circle only one number on the scale below)

10 9 8 7 6 5 4 3 2 1 0

Best Possible Quality of life

Worst Possible Quality of life

(as bad as or worse than being dead)

PATIENT'S QUESTIONNAIRE	QOLIE 31 Version 1.0 UK Part 2	Participant UTIN	Visit date
		__ __/__ __ __	DD /MMM /YYYY

These questions are about how you **FEEL** and how things have been for you during the **past 4 weeks**. For each question, please indicate the one answer that comes closest to the way you have been feeling.

How much time during the past 4 weeks……. *(Circle one number on each line)*

	All of the time	Most of the time	A good bit of the time	Some of the time	A little bit of the time	None of the time
2. Did you feel full of life?	1	2	3	4	5	6
3. Have you been a very nervous person?	1	2	3	4	5	6
4. Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
5. Have you felt calm and peaceful?	1	2	3	4	5	6
6. Did you have a lot of energy?	1	2	3	4	5	6
7. Have you felt downhearted and low?	1	2	3	4	5	6
8. Did you feel worn out?	1	2	3	4	5	6
9. Have you been a happy person?	1	2	3	4	5	6
10. Did you feel tired?	1	2	3	4	5	6
11. Have you worried about having another fit?	1	2	3	4	5	6
12. Did you have difficulty reasoning and solving problems (such as making plans, making decisions, learning new things)?	1	2	3	4	5	6
13. Has your health limited your social activities (such as visiting friends or close relatives)?	1	2	3	4	5	6

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PATIENT'S QUESTIONNAIRE	QOLIE 31 Version 1.0 UK Part 3	Participant UTIN	Visit date
		__ __/__ __ __	DD /MMM /YYYY

14. How has your **QUALITY OF LIFE** been during the **past 4 weeks** (that is, how have things been going for you)?

(Circle one number)

Very good could hardly have been better	Pretty good	Good & bad parts about equal	Pretty bad	Very bad: could hardly have been worse
1	2	3	4	5

The following question is about **MEMORY.**

(Circle one number)

	Yes, a lot	Yes, somewhat	Only a little	No, not at all
15. In the past 4 weeks, have you had any trouble with your memory?	1	2	3	4

The following question is about **how often** during the **past 4 weeks** you have had trouble remembering or **how often** this memory problem has interfered with your normal work or living

(Circle one number only for question 16)

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
16. Trouble remembering things people told you	1	2	3	4	5	6

PATIENT'S QUESTIONNAIRE	QOLIE – 31 Version 1.0 UK Part 4	Participant UTIN	Visit date
		__ __/__ __ __	__ /_____ /_____

The following questions are about **CONCENTRATION** problems you may have. During the **past 4 weeks, how often** have you had trouble concentrating or **how often** have these problems interfered with your normal work or living? *(Circle one number on each line)*

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
17. Trouble concentrating on reading	1	2	3	4	5	6
18. Trouble concentrating on one thing at a time	1	2	3	4	5	6

The following questions are about problems you may have with certain **ACTIVITIES**. Circle one number for **how much** during the **past 4 weeks** your epilepsy or antiepileptic medication has caused you trouble with…… *(Circle one number on each line)*

	A great deal	A lot	Somewhat	Only a little	No, not at all
19. Leisure time (such as hobbies and going out)	1	2	3	4	5
20. Driving	1	2	3	4	5

The following questions relate to how you **FEEL** about your **fits.** *(Circle one number on each line)*

	Very fearful	Somewhat fearful	Not very fearful	Not fearful at all
21. How afraid are you of having a fit during the next 4 weeks?	1	2	3	4

	Worry a lot	Occasionally worry	Don't worry at all
22. Do you worry about hurting yourself during a fit?	1	2	3

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PATIENT'S QUESTIONNAIRE	QOLIE – 31 Version 1.0 UK Part 5	Participant UTIN	Visit date
		_ _/_ _ _	DD /MMM /YYYY

The following questions relate to how you **FEEL** about your **fits.** *(Circle one number on each line)*

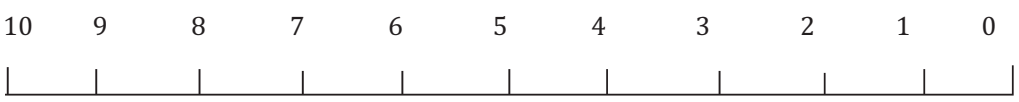
	Very worried	Somewhat worried	Not very worried	Not at all worried
23. How worried are you about embarrassment or other social problems due to a fit during the next 4 weeks?	**1**	**2**	**3**	**4**
24. How worried are you that the drugs you are taking may be bad for you if you have to take them for a long time?	**1**	**2**	**3**	**4**

For each of these **PROBLEMS** circle one number for **how much they bother you** on a scale of 1 to 5 where 1 = Not at all bothersome, and 5 = Extremely bothersome.

	Not at all bothersome				Extremely bothersome
25. Fits	**1**	**2**	**3**	**4**	**5**
26. Memory difficulties	**1**	**2**	**3**	**4**	**5**
27. Work limitations	**1**	**2**	**3**	**4**	**5**
28. Social limitations	**1**	**2**	**3**	**4**	**5**
29. Physical effects of antiepileptic drugs	**1**	**2**	**3**	**4**	**5**
30. Mental effects of antiepileptic drugs	**1**	**2**	**3**	**4**	**5**

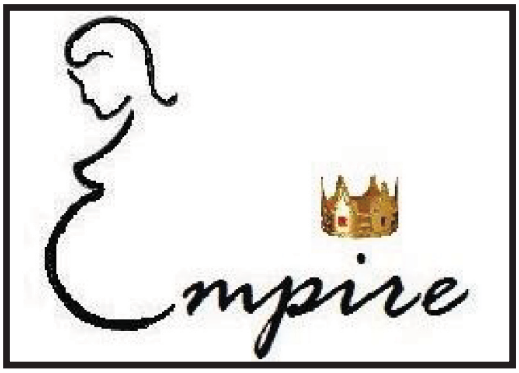
31. How good or bad do you think your health is? On the thermometer scale below, the best imaginable state of health is 10 and the worst imaginable state is 0. Please indicate how you feel about your health by circling one number on the scale. **Please consider your epilepsy as part of your health when you answer this question**.

(Please circle only one number on the scale below)



Best Imaginable Health State — Worst Imaginable Health State

Antenatal follow-up booklet



ANTENATAL FOLLOW-UP BOOKLET

Patient UTIN: __ __/__ __ __

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ANTENATAL FOLLOW-UP BOOKLET	Visit checklist Part 1	Participant UTIN	Visit date
		__ __/__ __ __	__ /__ /__ DD / MMM / YYYY

Gestational age	_____weeks _____days

CHECKLIST		ACTION
Have you received a PURPLE ALERT or requested any non trial serum AED levels?	**Yes** ☐	Check that serum AED levels collected since the participant's entry into the trial have been received from the trial office and have been recorded in **Purple Alert Form (PAF)**.
	No ☐	No action required
Has a blood sample been taken?	**Yes** ☐	Centrifuge and package sample according to SOP no.3 Blood collection and processing Send EMPIRE trial blood request form to trial office
	No ☐	Please take blood sample and package according to SOP no.3 Blood collection and processing Send EMPIRE trial blood request form to trial office Or Document reason why blood sample was not taken. ***Please state here:***
Has participant completed <u>all</u> relevant pages of the EMPIRE diary	**Yes** ☐	Please file diary in participant's CRF file and provide participant with a new diary Please enter next clinic visit date and time in participants diary.
	No ☐	Please ask participant to recall as much information since the last visit as possible and document in diary.
Has the participant completed: **Patient's questionnaire?**	**Yes** ☐	Return completed **Patient's questionnaire** to participant's CRF file.
	No ☐	Ask participant to complete **Patient's questionnaire** and file in participant's CRF file. OR Document reason why not completed ***Please state here:***

FOR PARTICIPANTS BETWEEN 32 - 36 WEEKS GESTATION ONLY **Has the participant completed:** **QOLIE questionnaire?**	**Yes** ☐	Return completed **Patient's questionnaire** to participant's CRF file.
	No ☐	Ask participant to complete **Patient's questionnaire** and file in participant's CRF file. OR Document reason why not completed ***Please state here:***

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ANTENATAL FOLLOW-UP BOOKLET	Visit checklist Part 2	Participant UTIN	Visit date
		__ __/__ __ __	DD /MMM /YYYY

CHECKLIST		ACTION
Have there been any dose changes to AED or concomitant medication?	**Yes** ☐	Please, if so note all the changes in relevant part of this booklet.
	No ☐	No further action
Has participant experienced any adverse events?	**Yes** ☐	Report in accordance with SOP no. 4. Adverse events and serious adverse events reporting. Update **Adverse Events Form**.
	No ☐	No further action
FOR PARTICIPANTS 20 WEEKS GESTATION ONLY **Has a routine ultrasound been conducted?**	**Yes** ☐	Please complete **Ultrasound form for congenital abnormalities in midtrimester** and file in participant's CRF file.
	No ☐	No further action.
FOR PARTICIPANTS 24 WEEKS & OVER ONLY **Is an ultrasound scan for fetal growth required?**	**Yes** ☐	Please complete **Ultrasound form for fetal growth** and file in participant's CRF file
	No ☐	No further action

ANTENATAL FOLLOW-UP BOOKLET	AED Medication Part 1	Participant UTIN	Visit date
		__ __/__ __ __	__ /___ /____

CURRENT TREATMENT

Current AED. Please use Brand name, if prescribed	Current daily dose (mg)	Does the dose need to be changed today?	New daily dose (mg)
carbamazepine (generic) **Yes** ☐ **No** ☐		**Yes** ☐ **No** ☐	
Tegretol (brand) **Yes** ☐ **No** ☐			
Tegretol Retard (brand) **Yes** ☐ **No** ☐			
lamotrigine (generic) **Yes** ☐ **No** ☐		**Yes** ☐ **No** ☐	
Lamictal (brand) **Yes** ☐ **No** ☐			
levetiracetam (generic) **Yes** ☐ **No** ☐		**Yes** ☐ **No** ☐	
Keppra (brand) **Yes** ☐ **No** ☐			
phenytoin (generic) **Yes** ☐ **No** ☐		**Yes** ☐ **No** ☐	
Epanutin (brand) **Yes** ☐ **No** ☐			
sodium valproate (generic) **Yes** ☐ **No** ☐		**Yes** ☐ **No** ☐	
Epilim (brand) **Yes** ☐ **No** ☐			

Have you adding any new AED medication today? *If **yes**, please update specify drug name (brand) and dose below*	**Yes** ☐ **No** ☐

Drug name:	**Daily dose (mg):**

If dose is being changed or a new drug added today, was this in response to? ***(please tick one)***

Purple alert ☐ Clinical concerns ☐ Patient concerns ☐

Has there been any change in the treatment between the last clinic visit and patient's visit today?

Yes ☐ **No** ☐ *If **yes**, please update* ***'TREATMENT MODIFICATION'*** **in next section'**

Since the last visit, has the team received a PURPLE ALERT for this patient?

Yes ☐ **No** ☐ *If **yes**, please fill the **PURPLE ALERT** section in the end of this booklet*

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ANTENATAL FOLLOW-UP BOOKLET	AED Medication Part 2	Participant UTIN	Visit date
		_ _/_ _ _	DD / MMM / YYYY

TREATMENT MODIFICATION SINCE LAST CLINICAL VISIT

CAUTION! Please record **all** changes in treatment in separate rows, alike if the change refers to dosage change, change of a drug's brand, drug discontinuation or commencement.

New drug or dosage change of already received one?	AED name	Daily dose before change* (mg)	Date of change, drug introduction or discontinuation	Daily dose after change or start dose in case of new drug (mg)	If dose changed since last visit, who made the change?	If dose changed since last visit, was this in response to? *(please tick one)?*
New drug ☐ Dose change ☐ Drug stopped ☐			DD / MMM / YYYY		Clinical team ☐ Patient ☐	Purple alert ☐ Clinical concerns ☐ Patient concerns ☐
New drug ☐ Dose change ☐ Drug stopped ☐			DD / MMM / YYYY		Clinical team ☐ Patient ☐	Purple alert ☐ Clinical concerns ☐ Patient concerns ☐
New drug ☐ Dose change ☐ Drug stopped ☐			DD / MMM / YYYY		Clinical team ☐ Patient ☐	Purple alert ☐ Clinical concerns ☐ Patient concerns ☐
New drug ☐ Dose change ☐ Drug stopped ☐			DD / MMM / YYYY		Clinical team ☐ Patient ☐	Purple alert ☐ Clinical concerns ☐ Patient concerns ☐
New drug or dosage change of already received one?	AED name	Daily dose before change* (mg)	Date of change, drug introduction or discontinuation	Daily dose after change or start dose in case of new drug (mg)	If dose changed since last visit, who made the change?	If dose changed since last visit, was this in response to? *(please tick one)?*
New drug ☐ Dose change ☐ Drug stopped ☐			DD / MMM / YYYY		Clinical team ☐ Patient ☐	Purple alert ☐ Clinical concerns ☐ Patient concerns ☐

ANTENATAL FOLLOW-UP BOOKLET	Adherence checklist Part 1	Participant UTIN	Visit date
		__ __/__ __ __	__ /__ /__ (DD / MMM / YYYY)

TREATMENT ADHERENCE

Has the patient taken the Trial AED(s) according to the clinician's plan?	Yes ☐ No ☐ *If **no**, please select **one** relevant reason:*
Concerned about effects to baby	☐
Concerned about side effects	☐
Forgotten to change dose	☐
Instructions not clear	☐
Has the AED serum level been checked by anyone outside the trial protocol?	Yes ☐ No ☐

If yes please specify by whom and record serum level(s) below:

A & E	☐	Obstetrician	☐	Neurologist	☐	Midwife	☐

Date of Blood Test	AED Medication	Test result for serum level		
		Value	Unit	
__ /__ /__ (DD / MMM / YY)			µmol/l ☐	mg/l ☐
__ /__ /__ (DD / MMM / YY)			µmol/l ☐	mg/l ☐
__ /__ /__ (DD / MMM / YY)			µmol/l ☐	mg/l ☐
__ /__ /__ (DD / MMM / YY)			µmol/l ☐	mg/l ☐
__ /__ /__ (DD / MMM / YY)			µmol/l ☐	mg/l ☐

If yes, please report the unblinding to Trial Coordinator

HOSPITAL ADMISSION

Has the patient been admitted to hospital since her last visit?					Yes ☐ No ☐		Was it epilepsy related?
Admission 1	Date & Time of admission	__ /__ /__ (DD / MMM / YY)	__ : __ (HH : MM)	Date & Time of discharge	__ /__ /__ (DD / MMM / YY)	__ : __ (HH : MM)	Yes ☐ No ☐
Admission 2	Date & Time of admission	__ /__ /__ (DD / MMM / YY)	__ : __ (HH : MM)	Date & Time of discharge	__ /__ /__ (DD / MMM / YY)	__ : __ (HH : MM)	Yes ☐ No ☐
Admission 3	Date & Time of admission	__ /__ /__ (DD / MMM / YY)	__ : __ (HH : MM)	Date & Time of discharge	__ /__ /__ (DD / MMM / YY)	__ : __ (HH : MM)	Yes ☐ No ☐
Admission 4	Date & Time of admission	__ /__ /__ (DD / MMM / YY)	__ : __ (HH : MM)	Date & Time of discharge	__ /__ /__ (DD / MMM / YY)	__ : __ (HH : MM)	Yes ☐ No ☐
Admission 5	Date & Time of admission	__ /__ /__ (DD / MMM / YY)	__ : __ (HH : MM)	Date & Time of discharge	__ /__ /__ (DD / MMM / YY)	__ : __ (HH : MM)	Yes ☐ No ☐

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ANTENATAL FOLLOW-UP BOOKLET	Non-AE medication	Participant UTIN	Visit date
		__/___	DD / MMM / YYYY

ADDITIONAL MEDICATION

This part is to be used to document all dose changes for **all** **non-AE medication** taken from the start of the trial up until the visit.

Medication	Total daily dose (mg)	Start date	Ongoing?	End date
Folic Acid		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
Vitamin K		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
Methyldopa		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
Nifedipine		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
Insulin		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
Metformin		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
Labetelol		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
Ferrous sulphate		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
Aspirin		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
Diazepam or clobazam		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
If any OTHER non-AED medication (other than listed above) is being used, please specify medication's name and fill in following gaps:				
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY

ANTENATAL FOLLOW-UP BOOKLET	Ultrasound form for congenital abnormalities in midtrimester	Participant UTIN	Date
		_ _/_ _ _	DD /MMM /YYYY

Was an ultrasound performed?		**Yes** ☐ **No** ☐ *If **yes**, please complete the following:*	
Is the pregnancy multiple?	**Yes** ☐ **No** ☐	*If **yes**, please specify* ☐ **Twins** ☐ **Triplets** ☐ **More**	
Fetus (no.)		**Gestational Age**	_____weeks _____days
Congenital malformations	**Yes** ☐ **No** ☐ *If **yes**, please specify below*		
Spina bifida	**Yes** ☐ **No** ☐	**Hydrocephalus**	**Yes** ☐ **No** ☐
Diaphragmatic hernia	**Yes** ☐ **No** ☐	**Anencephaly**	**Yes** ☐ **No** ☐
Cleft lip	**Yes** ☐ **No** ☐	**Congenital heart disease**	**Yes** ☐ **No** ☐
Cleft palate	**Yes** ☐ **No** ☐	**Tumours**	**Yes** ☐ **No** ☐
Gastroschisis	**Yes** ☐ **No** ☐	**Limb abnormalities**	**Yes** ☐ **No** ☐
Duodenal atresia	**Yes** ☐ **No** ☐	**External genital abnormalities**	**Yes** ☐ **No** ☐
Congenital Cystic Adenomatoid Malformation	**Yes** ☐ **No** ☐	**Other, please specify:**	**Yes** ☐ **No** ☐
Was a fetal echo performed?		**Yes** ☐ **No** ☐ **Not done** ☐	
*If **yes**,* please specify if fetal echo was: Normal ☐ Abnormal ☐		**If abnormal, please specify abnormality:**	
Fetus (no.)		**Gestational Age**	_____weeks _____days
Congenital malformations	**Yes** ☐ **No** ☐ *If **yes**, please specify below*		
Spina bifida	**Yes** ☐ **No** ☐	**Hydrocephalus**	**Yes** ☐ **No** ☐
Diaphragmatic hernia	**Yes** ☐ **No** ☐	**Anencephaly**	**Yes** ☐ **No** ☐
Cleft lip	**Yes** ☐ **No** ☐	**Congenital heart disease**	**Yes** ☐ **No** ☐
Cleft palate	**Yes** ☐ **No** ☐	**Tumours**	**Yes** ☐ **No** ☐
Gastroschisis	**Yes** ☐ **No** ☐	**Limb abnormalities**	**Yes** ☐ **No** ☐
Duodenal atresia	**Yes** ☐ **No** ☐	**External genital abnormalities**	**Yes** ☐ **No** ☐
Congenital Cystic Adenomatoid Malformation	**Yes** ☐ **No** ☐	**Other, please specify:**	**Yes** ☐ **No** ☐
Was a fetal echo performed?		**Yes** ☐ **No** ☐ **Not done** ☐	
*If **yes**,* please specify if fetal echo was: Normal ☐ Abnormal ☐		**If abnormal, please specify abnormality:**	

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ANTENATAL FOLLOW-UP BOOKLET	Ultrasound form for fetal growth	Participant UTIN	Date
		__ __/__ __ __	__ /MMM /YYYY

Was fetal growth measured?		**Yes** ☐ **No** ☐ *If **yes**, please complete the following*		
Date of scan		__ /MMM /YYYY		
Is the pregnancy multiple?		**Yes** ☐ **No** ☐	*If **yes**, please specify* ☐ **Twins** ☐ **Triplets** ☐ **More**	
Fetus number		**Gestational Age**	_____weeks _____days	
Small for Gestational Age *(defined as birth weight less than 10th centile)*	**Yes** ☐ **No** ☐	**Customised centile used**	**Yes** ☐ **No** ☐	
Umbilical artery Doppler	Normal		☐	
	Absent end diastolic flow (EDF)		☐	
	Reversed end diastolic flow (EDF)		☐	
	Raised pulsatility index		☐	
Liquor volume	Normal		☐	
	Reduced		☐	
	Excess		☐	
Fetus number		**Gestational Age**	_____weeks _____days	
Small for Gestational Age *(defined as birth weight less than 10th centile)*	**Yes** ☐ **No** ☐	**Customised centile used**	**Yes** ☐ **No** ☐	
Umbilical artery Doppler	Normal		☐	
	Absent end diastolic flow (EDF)		☐	
	Reversed end diastolic flow (EDF)		☐	
	Raised pulsatility index		☐	
Liquor volume	Normal		☐	
	Reduced		☐	
	Excess		☐	

ANTENATAL FOLLOW-UP BOOKLET	Purple alert record	Participant UTIN	Date
		__ __/__ __ __	DD /MMM /YYYY

Please, fill this section only if you received a PURPLE ALERT for this patient since the last clinical visit.

If you received PURPLE ALERT for this patient, did you inform the patient about it?	**Yes** ☐ **No** ☐
*If you **did not** inform the patient, please give reason below:*	
What action was taken as a result of the PURPLE alert?	
a. Offer to patient to increase AED dose	**Yes** ☐ **No** ☐
*If **yes**, did patient accept increase in dose?*	**Yes** ☐ **No** ☐
*If you **did not** offer an increase in dose, please give reason below:*	
b. Follow-up visit brought forward	**Yes** ☐ **No** ☐
c. Other action taken	**Yes** ☐ **No** ☐
*If **yes**, please specify:*	

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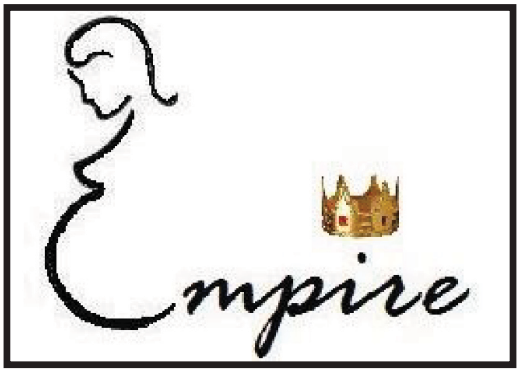
Delivery booklet



DELIVERY BOOKLET

Patient UTIN: _ _/_ _ _

DELIVERY BOOKLET	Visit checklist	Participant UTIN	**Visit date**
		__ __/__ __ __	__ /__ /__ DD /MMM /YYYY

CHECKLIST		**ACTION**
Has a blood sample been taken?	**Yes** ☐	Centrifuge and package sample according to Blood Processing SOP no.3 Send EMPIRE trial blood request form to trial office
	No ☐	Please take blood sample and package according to Blood Processing SOP no.3 Send EMPIRE trial blood request form to trial office Or Document reason why blood sample was not taken ***Please state here:***
Has the cord blood sample been taken?	**Yes** ☐	Centrifuge and package sample according to Blood Processing SOP no.3 Send EMPIRE trial blood request form to trial office
	No ☐	Please take cord blood sample and package according to Blood Processing SOP no.3 Send EMPIRE trial blood request form to trial office Or Document reason why the sample was not taken ***Please state here:***
Has cord pH sample been taken?	**Yes** ☐	Documented result in CRF.
	No ☐	Take cord pH according to routine practice at site and document the result in CRF. Or Document reason why the sample was not taken ***Please state here:***
Have the delivery booklet been completed?	**Yes** ☐	File **Delivery Booklet** is in participant's CRF file.
	No ☐	Complete **Delivery Booklet** and file in participant's CRF file

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DELIVERY BOOKLET	Delivery details	Participant UTIN	Visit date
		_ _/_ _ _	DD /MMM /YYYY

DELIVERY DETAILS

Gestational age at delivery	_____weeks _____days
Delivery mode	**Spontaneous Vaginal** ☐ **Forceps** ☐ **Ventouse** ☐ **Caesarean Section** ☐

MATERNAL COMPLICATIONS

Pre-clampsia	**Yes** ☐ **No** ☐	**Gestation Diabetes Mellitus**	**Yes** ☐ **No** ☐	**Blood transfusion**	**Yes** ☐ **No** ☐
Preterm delivery (<37 weeks)		**Yes** ☐ **No** ☐	***If yes,*** **Spontaneous** ☐ **Induced** ☐		
Post partum haemorrhage		**Yes** ☐ **No** ☐	***If yes,*** **Atonic** ☐ **Trauma** ☐ **Both** ☐		
Ante partum haemorrhage		**Yes** ☐ **No** ☐	**Preterm rupture of membranes (<37 weeks)**		**Yes** ☐ **No** ☐
Induction of labour *(If yes, please specify reasons for induction)*		**Yes** ☐ **No** ☐	Seizure deterioration Post dates Pre-eclampsia Maternal request Spontaneous rupture of the membranes		**Yes** ☐ **No** ☐ **Yes** ☐ **No** ☐ **Yes** ☐ **No** ☐ **Yes** ☐ **No** ☐ **Yes** ☐ **No** ☐
Admission to HDU/ITU		**Yes** ☐ **No** ☐	*If **yes**, was it **seizure related?***		**Yes** ☐ **No** ☐
Infection *(if yes, please specify)*		**Yes** ☐ **No** ☐	Genital Urinary Chorioamnionitis Wound Respiratory Other (*if yes, please specify below*)		**Yes** ☐ **No** ☐ **Yes** ☐ **No** ☐ **Yes** ☐ **No** ☐ **Yes** ☐ **No** ☐ **Yes** ☐ **No** ☐ **Yes** ☐ **No** ☐
Any other maternal complications		**Yes** ☐ **No** ☐	*If **yes**, please specify*		

HOSPITAL ADMISSION

Date & Time of admission	DD / MMM / YY	HH : MM	**Date & Time of discharge**	DD / MMM / YY	HH : MM

BREASTFEEDING INTENTION

Sole breast feeding	☐	**Mixed breast & bottle**	☐	**Bottle only**	☐

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DELIVERY BOOKLET	Baby details	Participant UTIN	Visit date
		__ __/__ __ __	__ /__ /____

BABY DETAILS

Please use the following sheets to document information about all of the participant's births/children. One sheet should be used per child. Please specify child number between booklet name and participant UTIN.

Birth Weight		**kg**	**Baby's sex**	**Female** ☐ **Male** ☐	
Birth weight in customised centiles			**_____ centiles**	**Head Circumference**	**cm**
Apgar score	**1'**		**Cord pH**	**A**	
	5'			**V**	

Stillbirth	**Yes** ☐ **No** ☐	**Neo-natal death**	**Yes** ☐ **No** ☐
Small for gestational age *(defined as weight less than 10th centile)*	**Yes** ☐ **No** ☐	**Admission to neonatal unit**	**Yes** ☐ **No** ☐

CONGENITAL MALFORMATIONS						
Diaphragmatic hernia	**Yes** ☐ **No** ☐	**Gastroschisis**	**Yes** ☐ **No** ☐	**Hydrocephalus**	**Yes** ☐ **No** ☐
Spina bifida	**Yes** ☐ **No** ☐	**Duodenal atresia**	**Yes** ☐ **No** ☐	**Cleft lip**	**Yes** ☐ **No** ☐
Cleft palate	**Yes** ☐ **No** ☐	**Congenital Cystic Adenomatoid Malformation**	**Yes** ☐ **No** ☐	**Anencephaly**	**Yes** ☐ **No** ☐
Congenital heart disease	**Yes** ☐ **No** ☐	*If yes, please specify*			
Tumours	**Yes** ☐ **No** ☐	*If yes, please specify*			
Limb abnormalities	**Yes** ☐ **No** ☐	*If yes, please specify*			
External genital abnormities	**Yes** ☐ **No** ☐	*If yes, please specify*			
Any other malformation	**Yes** ☐ **No** ☐	*If yes, please specify*			

DELIVERY BOOKLET	Baby details	Participant UTIN	Visit date
		__ __/__ __ __	DD /MMM /YYYY

BABY DETAILS

Please use the following sheets to document information about all of the participant's births/children. One sheet should be used per child. Please specify child number between booklet name and participant UTIN.

Birth Weight		**kg**	**Baby's gender**	**Female** ☐ **Male** ☐	
Birth weight in customised centiles			**_____ centiles**	**Head Circumference**	**cm**
Apgar score	**1'**		**Cord pH**	**A**	
	5'			**V**	

Stillbirth	**Yes** ☐ **No** ☐	**Neo-natal death**	**Yes** ☐ **No** ☐
Small for gestational age *(defined as weight less than 10th centile)*	**Yes** ☐ **No** ☐	**Admission to neonatal unit**	**Yes** ☐ **No** ☐

CONGENITAL MALFORMATIONS								
Diaphragmatic hernia	**Yes** ☐	**No** ☐	**Gastroschisis**	**Yes** ☐	**No** ☐	**Hydrocephalus**	**Yes** ☐	**No** ☐
Spina bifida	**Yes** ☐	**No** ☐	**Duodenal atresia**	**Yes** ☐	**No** ☐	**Cleft lip**	**Yes** ☐	**No** ☐
Cleft palate	**Yes** ☐	**No** ☐	**Congenital Cystic Adenomatoid Malformation**	**Yes** ☐	**No** ☐	**Anencephaly**	**Yes** ☐	**No** ☐
Congenital heart disease	**Yes** ☐	**No** ☐	*If yes, please specify*					
Tumours	**Yes** ☐	**No** ☐	*If yes, please specify*					
Limb abnormalities	**Yes** ☐	**No** ☐	*If yes, please specify*					
External genital abnormities	**Yes** ☐	**No** ☐	*If yes, please specify*					
Any other malformation	**Yes** ☐	**No** ☐	*If yes, please specify*					

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DELIVERY BOOKLET	Baby details	Participant UTIN	Visit date
		_ _/_ _ _	DD /MMM /YYYY

BABY DETAILS

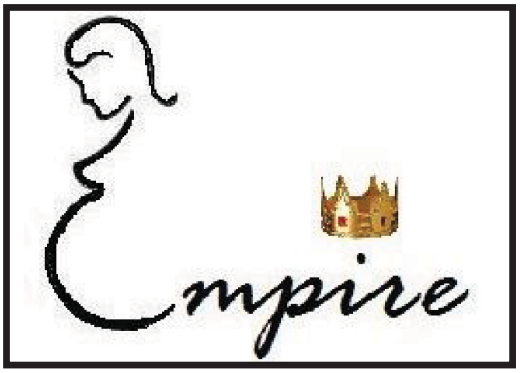
Please use the following sheets to document information about all of the participant's births/children. One sheet should be used per child. Please specify child number between booklet name and participant UTIN.

Birth Weight		**kg**	**Baby's gender**	**Female** ☐ **Male** ☐	
Birth weight in customised centiles			**_____ centiles**	**Head Circumference**	**cm**
Apgar score	**1'**		**Cord pH**	**A**	
	5'			**V**	

Stillbirth	**Yes** ☐ **No** ☐	**Neo-natal death**	**Yes** ☐ **No** ☐
Small for gestational age *(defined as weight less than 10th centile)*	**Yes** ☐ **No** ☐	**Admission to neonatal unit**	**Yes** ☐ **No** ☐

CONGENITAL MALFORMATIONS						
Diaphragmatic hernia	**Yes** ☐ **No** ☐	**Gastroschisis**	**Yes** ☐ **No** ☐	**Hydrocephalus**	**Yes** ☐ **No** ☐	
Spina bifida	**Yes** ☐ **No** ☐	**Duodenal atresia**	**Yes** ☐ **No** ☐	**Cleft lip**	**Yes** ☐ **No** ☐	
Cleft palate	**Yes** ☐ **No** ☐	**Congenital Cystic Adenomatoid Malformation**	**Yes** ☐ **No** ☐	**Anencephaly**	**Yes** ☐ **No** ☐	
Congenital heart disease	**Yes** ☐ **No** ☐	*If yes, please specify*				
Tumours	**Yes** ☐ **No** ☐	*If yes, please specify*				
Limb abnormalities	**Yes** ☐ **No** ☐	*If yes, please specify*				
External genital abnormities	**Yes** ☐ **No** ☐	*If yes, please specify*				
Any other malformation	**Yes** ☐ **No** ☐	*If yes, please specify*				

Postnatal follow-up booklet



POSTNATAL FOLLOW-UP BOOKLET

Patient UTIN: __ __/__ __ __

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POSTNATAL FOLLOW-UP BOOKLET	Visit checklist	Participant UTIN	Visit date
		_ _/_ _ _	DD /MMM /YYYY

CHECKLIST		ACTION
Has a blood sample been taken?	**Yes** ☐	Send EMPIRE trial blood request form to trial office Centrifuge and package sample according to SOP no.3 Blood collection and processing
	No ☐	Centrifuge and package sample according to SOP no.3 Blood collection and processing Send EMPIRE trial blood request form to trial office Or Document reason why blood sample was not taken. ***Please state here:***
Has the participant completed: **Patient's questionnaire?**	**Yes** ☐	Return completed **Patient's questionnaire** to participant's CRF file.
	No ☐	Ask participant to complete **Patient's questionnaire** and file in participant's CRF file. OR Document reason why not completed ***Please state here:***
Have there been any dose changes to AED or concomitant medication?	**Yes** ☐	Please, if so note all the changes in relevant part of this booklet.
	No ☐	No further action
Has participant experienced any adverse events?	**Yes**	Report in accordance with SOP no. 4. Adverse events and serious adverse events reporting. Update **Adverse Events Form**.
	No	No further action

POSTNATAL FOLLOW-UP BOOKLET	Post Natal Form	Participant UTIN	Visit date
		__ __/__ __ __	__ /MMM /YYYY

Please use the following sheets to document information about all of the participant's births/children. One sheet should be used per child. Please specify child number between booklet name and participant UTIN.

NEONATAL DEATH

Neonatal death	**Yes** ☐ **No** ☐		
Date of neonatal death	DD /MMM /YYYY		
Reasons for neonatal death *(please tick all relevant reasons)*	**Congenital abnormalities**		☐
	Infection		☐
	Birth trauma		☐
	Extreme prematurity		☐
	Other	*If **other**, please specify:*	☐

BABY DETAILS

Age (n/52)		**Weight**	kg	**Head Circumference**	cm
Any maternal concerns	**Yes** ☐ **No** ☐ *If **yes**, please specify below:*				
Admission to neonatal unit after discharge	**Yes** ☐ **No** ☐ *If **yes**, please specify below:*				
Baby has been in neonatal unit since birth	**Yes** ☐ **No** ☐			**Baby has congenital abnormalities**	**Yes** ☐ **No** ☐

BREASTFEEDING

Current feeding method		Duration of sole breastfeeding
Sole breast feeding	☐	
Mixed breast & bottle	☐	Weeks_____ Days_____
Bottle only	☐	Weeks_____ Days_____

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POSTNATAL FOLLOW-UP BOOKLET	Post Natal Form	Participant UTIN	Visit date
		__ __/__ __ __	__ /__MMM /__YYYY

Please use the following sheets to document information about all of the participant's births/children. One sheet should be used per child. Please specify child number between booklet name and participant UTIN.

NEONATAL DEATH

Neonatal death	**Yes** ☐ **No** ☐		
Date of neonatal death	__ /__MMM /__YYYY		
Reasons for neonatal death *(please tick all relevant reasons)*	**Congenital abnormalities**		☐
	Infection		☐
	Birth trauma		☐
	Extreme prematurity		☐
	Other	**Please specify:**	☐

BABY DETAILS

Age (n/52)		**Weight**	kg	**Head Circumference**	cm
Any maternal concerns	**Yes** ☐ **No** ☐ *If **yes**, please specify*				
Admission to neonatal unit after discharge	**Yes** ☐ **No** ☐ *If **yes**, please specify*				
Baby has been in neonatal unit since birth	**Yes** ☐ **No** ☐				
Baby has congenital abnormalities	**Yes** ☐ **No** ☐				

BREASTFEEDING

Current feeding method		Duration of sole breastfeeding
Sole breast feeding	☐	
Mixed breast & bottle	☐	Weeks_____ Days_____
Bottle only	☐	Weeks_____ Days_____

POSTNATAL FOLLOW-UP BOOKLET	Post Natal Form	Participant UTIN	Visit date
		__ __/__ __ __	__ /__ /__

Please use the following sheets to document information about all of the participant's births/children. One sheet should be used per child. Please specify child number between booklet name and participant UTIN.

NEONATAL DEATH

Neonatal death	**Yes** ☐ **No** ☐		
Date of neonatal death	__ /__ /__		
Reasons for neonatal death *(please tick all relevant reasons)*	**Congenital abnormalities**		☐
	Infection		☐
	Birth trauma		☐
	Extreme prematurity		☐
	Other	**Please specify:**	☐

BABY DETAILS

Age (n/52)		**Weight**	kg	**Head Circumference**	cm
Any maternal concerns	**Yes** ☐ **No** ☐ *If **yes**, please specify*				
Admission to neonatal unit after discharge	**Yes** ☐ **No** ☐ *If **yes**, please specify*				
Baby has been in neonatal unit since birth	**Yes** ☐ **No** ☐				
Baby has congenital abnormalities	**Yes** ☐ **No** ☐				

BREASTFEEDING

Current feeding method		Duration of sole breastfeeding
Sole breast feeding	☐	
Mixed breast & bottle	☐	Weeks_____ Days_____
Bottle only	☐	Weeks_____ Days_____

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POSTNATAL FOLLOW-UP BOOKLET	Adherence checklist Part 1	Participant UTIN	Visit date
		__ __/__ __ __	DD /MMM /YYYY

CURRENT AED

Current AED Please use Brand name, if prescribed		Current daily dose (mg)	Date of any dose change after delivery
carbamazepine (generic)	Yes ☐ No ☐		DD /MMM /YY
Tegretol	Yes ☐ No ☐		DD /MMM /YY
Tegretol Retard	Yes ☐ No ☐		DD /MMM /YY
lamotrigine (generic)	Yes ☐ No ☐		DD /MMM /YY
Lamictal (brand)	Yes ☐ No ☐		DD /MMM /YY
levetiracetam (generic)	Yes ☐ No ☐		DD /MMM /YY
Keppra (brand)	Yes ☐ No ☐		DD /MMM /YY
phenytoin (generic)	Yes ☐ No ☐		DD /MMM /YY
Epanutin (brand)	Yes ☐ No ☐		DD /MMM /YY
sodium valproate (generic)	Yes ☐ No ☐		DD /MMM /YY
Epilim (brand)	Yes ☐ No ☐		DD /MMM /YY

Has there been an AED dose change since delivery?	**Yes** ☐ **No** ☐
If the dose has been changed since delivery:	
1) Who was responsible for the change:	**Clinician** ☐ **Patient** ☐
2) Was it in response to: *(please tick all relevant reasons)*	**Routine clinical plan** ☐ **Patient concerns** ☐ **Clinician concerns** ☐

Has the patient taken the AED postnatally according clinician's plan? *If **no**, please select one relevant reason:*	**Yes** ☐ **No** ☐
Concerned about worsening of seizures	☐
Forgotten to change dose	☐
Instructions not clear	☐

POSTNATAL FOLLOW-UP BOOKLET	Adherence checklist Part 2	Participant UTIN	Visit date
		_ _/_ _ _	DD / MMM / YYYY

AED LEVELS

Has the AED level been checked postnatally by anyone outside the EMPIRE Trial team? *If yes, please specify below:*							Yes ☐ No ☐	
A & E	☐	Obstetrician	☐	Neurologist	☐		Midwife	☐
Has the result been revealed to the local research team?							Yes ☐ No ☐	

Date of Blood Test	AED Medication	Test result for serum level		
		Value	Unit	
DD / MMM / YY			µmol/l ☐	mg/l ☐
DD / MMM / YY			µmol/l ☐	mg/l ☐
DD / MMM / YY			µmol/l ☐	mg/l ☐
DD / MMM / YY			µmol/l ☐	mg/l ☐
DD / MMM / YY			µmol/l ☐	mg/l ☐
If yes, please report the unblinding to Trial Coordinator				

ANY ADDITIONAL MEDICATION

Medication	Total daily dose (mg)	Start date	Ongoing?	End date
Diazepam or clobazam		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY
		DD / MMM / YYYY	Yes ☐ No ☐	DD / MMM / YYYY

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POSTNATAL FOLLOW-UP BOOKLET	Adherence checklist Part 3	Participant UTIN	Visit date
		__ __/__ __ __	DD /MMM /YYYY

HOSPITAL ADMISSION

Has the patient been admitted to hospital since delivery?					Yes ☐ No ☐		Was it epilepsy related?	
Admission 1	Date & Time of admission	DD /MMM /YY	HH :MM	Date & Time of discharge	DD /MMM /YY	HH :MM	Yes ☐	No ☐
Admission 2	Date & Time of admission	DD /MMM /YY	HH :MM	Date & Time of discharge	DD /MMM /YY	HH :MM	Yes ☐	No ☐
Admission 3	Date & Time of admission	DD /MMM /YY	HH :MM	Date & Time of discharge	DD /MMM /YY	HH :MM	Yes ☐	No ☐
Admission 4	Date & Time of admission	DD /MMM /YY	HH :MM	Date & Time of discharge	DD /MMM /YY	HH :MM	Yes ☐	No ☐

TOXICITY

Did AED toxicity occur at any point during 6 weeks post delivery?	Yes ☐ No ☐
Did any of the following symptoms occur?	
dizziness	Yes ☐ No ☐
unsteadiness	Yes ☐ No ☐
nausea	Yes ☐ No ☐
headache	Yes ☐ No ☐
vomiting	Yes ☐ No ☐
Did toxicity result in medical intervention?	
Yes ☐ No ☐ *If **yes**, please specify:*	
☐ Admission to ward	☐ Change in medication
☐ Out-patient or GP appointment	☐ Seen and discharged at A&E
☐ Admission to ICU	☐ Telephone advice
☐ Other *(if yes, please specify)*	

Purple alert form

PURPLE ALERT FORM (PAF)	Participant UTIN	Date
	__/___	DD /MMM /YYYY

If you receive a purple alert for this participant please complete serum AED levels below:

If you are using a pre-trial serum level (PTSL) for this participant at baseline please ensure you document this as the first serum level on this form.

Pre-trial Serum AED Level as trial target level *(please tick one)*	Date of blood test	Current AED	Total daily dose (mg)	Serum Level		
				Value	Unit	
PPSL ☐ EPSL ☐ Neither ☐	DD /MMM /YYYY				µmol/l ☐ mg/l ☐	

IN TRIAL SERUM AED LEVELS				
Date of blood test	Most recent serum AED level (if available)			
	Current AED	Total daily dose (mg)	Serum Level	
			Value	Unit
DD /MMM /YYYY				µmol/l ☐ mg/l ☐
DD /MMM /YYYY				µmol/l ☐ mg/l ☐
DD /MMM /YYYY				µmol/l ☐ mg/l ☐
DD /MMM /YYYY				µmol/l ☐ mg/l ☐
DD /MMM /YYYY				µmol/l ☐ mg/l ☐
DD /MMM /YYYY				µmol/l ☐ mg/l ☐
DD /MMM /YYYY				µmol/l ☐ mg/l ☐
DD /MMM /YYYY				µmol/l ☐ mg/l ☐

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DD / MMM / YYYY				µmol/l ☐ mg/l ☐
DD / MMM / YYYY				µmol/l ☐ mg/l ☐
DD / MMM / YYYY				µmol/l ☐ mg/l ☐

PURPLE ALERT FORM (PAF)	Participant UTIN	Date
	__ __/__ __ __	DD / MMM / YYYY

If you receive a purple alert for this participant please complete serum AED levels below:

If you are using a pre-trial serum level (PTSL) for this participant at baseline please ensure you document this as the first serum level on this form.

Pre-trial Serum AED Level as trial target level *(please tick one)*	Date of blood test	Current AED	Total daily dose (mg)	Serum Level		
				Value	Unit	
PPSL ☐ EPSL ☐ Neither ☐	DD / MMM / YYYY				µmol/l mg/l	☐ ☐

IN TRIAL SERUM AED LEVELS

Date of blood test	Most recent serum AED level (if available)			
	Current AED	Total daily dose (mg)	Serum Level	
			Value	Unit
DD / MMM / YYYY				µmol/l ☐ mg/l ☐
DD / MMM / YYYY				µmol/l ☐ mg/l ☐
DD / MMM / YYYY				µmol/l ☐ mg/l ☐
DD / MMM / YYYY				µmol/l ☐ mg/l ☐
DD / MMM / YYYY				µmol/l ☐ mg/l ☐
DD / MMM / YYYY				µmol/l ☐ mg/l ☐
DD / MMM / YYYY				µmol/l ☐ mg/l ☐
DD / MMM / YYYY				µmol/l ☐ mg/l ☐

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DD / MMM / YYYY				µmol/l ☐ mg/l ☐
DD / MMM / YYYY				µmol/l ☐ mg/l ☐
DD / MMM / YYYY				µmol/l ☐ mg/l ☐

Adverse events form

ADVERSE EVENTS* FORM	Participant UTIN
	__ __/__ __ __

*Refer to SOP no. 4 (AE and Serious AE Reporting) for further actions required if participant experiences an **AE**.

Adverse event (AE)		**Date reported**	DD /MMM /YYYY
AE timeframe	**AE onset date** DD / MMM / YYYY	**AE end date**	DD / MMM / YYYY
Intensity	☐ Mild ☐ Moderate ☐ Severe	**Serious AE**	☐ Serious ☐ Non serious
Is the AE likely to be due to the intervention?	☐ Yes ☐ No	**Is the AE expected?** *Expected reactions will be found in SmPC (http://emc.medicines.org.uk/) and/or protocol.*	☐ Yes ☐ No
Outcome of AE	☐ Resolved ☐ Resolved with sequelae (*If yes, specify)* ☐ Improved ☐ Persisting ☐ Worsened ☐ Fatal (*if yes, specify date of death* DD /MMM /YYYY*)* ☐ Unknown		

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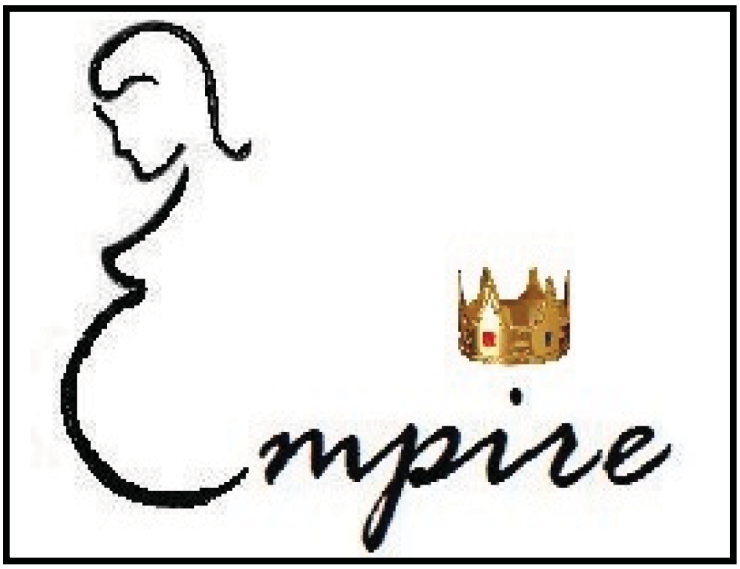
Appendix 10 Seizure diary

My EMPIRE diary



AntiEpileptic drug Monitoring in PREgnancy: an evaluation of effectiveness, cost-effectiveness and acceptability of monitoring strategies

Participant UTIN __ __/__ __ __

Next clinic appointment	DD/MMM/YYYY	HH:MM

Trials Office: Women's Health Research Unit, Centre for Primary Care and Public Health,
Blizard Institute, Barts and The London School of Medicine and Dentistry
Yvonne Carter Building, 58 Turner Street, London, E1 2AB. Tel: XXXX
Fax: XXXX

How do I use my EMPIRE diary?

There are 3 main sections to the trial diary that we ask that you complete. They are:

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- Seizure page……..Pages 4 & 5

At your first clinic appointment your doctor will discuss your seizures with you. You will both agree a code for your seizures, which you can easily enter into the seizure page of the diary. (Please see page 3 for a key of seizure codes). If you experience more than one type of seizure a different code will be agreed for each type of seizure.

The first date entered onto the seizure page will be the day of your first clinic appointment.

On days when you experience seizures we ask that you circle "Yes" in the "Seizures" box of the seizure page. Please enter the agreed code for your seizures in the "seizure code" column and the number of times you have experienced that seizure in the "Number of seizures today" column.

On days when you **do not** experience seizures please circle "No" in the "Seizures" box of your diary.

- Illness, injury or side effects……..Page 6

If you have any illnesses, injuries or side effects during the trial in please record these on this page. Please record the date and a description of the illness, injury and side effects.

- Changes in seizures……Page 6

If you notice any changes in you seizures, for example, unusually severe seizures or seizures you do not usually experience please record these on this page. Please record the date and a description of change in your seizures.

What if I forget to update my diary?

If at any point you forget to update your diary, please update it as soon as possible with as much information you can remember. However, if you cannot remember this information please circle "Not done".

What if I have any questions?

Please contact a member of the research team on:

Name:…….. Tel:……

Standard seizure codes

These are the standard seizure codes that are being used for the EMPIRE trial:

Code	Seizure description
A	Tonic-clonic seizures These are the seizures most people think of as epilepsy. At the start of the seizure: • the person becomes unconscious; their body goes stiff and if they are standing up they usually fall backwards; they may cry out; and they may bite their tongue or cheek. During the seizure: • they jerk and shake (convulse) as their muscles relax and tighten rhythmically; their breathing might be affected and become difficult or sound noisy; their skin may change colour and become very pale or bluish; and they may wet themselves. After the seizure (once the jerking stops): • their breathing and colour return to normal; and they may feel tired, confused, have a headache and want to sleep A tonic-clonic seizure can arise from seizures spread from one part of the brain (secondary generalised) or arise simultaneously from the whole brain (primary generalised).
B	Absence seizures Absences can happen very frequently. During an absence the person becomes unconscious for a short time. They may look blank and stare or their eyelids might flutter. They will not respond to what is happening around them. During typical absences, the person becomes blank and unresponsive for a few seconds. Because the seizures are so brief, they may go unnoticed.
C	Myoclonic seizures Myoclonic means 'muscle jerk'. Muscle jerks are not always due to epilepsy (for example, some people have them as they fall asleep). Myoclonic seizures are brief but can happen in clusters (many happening close together in time), and often happen shortly after waking. The person is conscious
D	Simple partial seizures (SPS) Only a small part of the brain is affected. The person is conscious (aware and alert) and will usually know that something is happening. What happens to the person depends on where in the brain the seizure happens.
E	Complex partial seizures (CPS) The person's consciousness is affected; they may be confused, and afterwards may have no memory of the seizure. They might be able to hear, but might not fully understand what has been said or be able to respond. They might make strange or repetitive movements that have no purpose(called 'automatisms').
F	Other **Clonic seizures** - Some people have convulsive seizures but their body does not go stiff at the start. These are called clonic seizures.

My seizure code(s)

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Monday		Tuesday		Wednesday		Thursday		Friday		Saturday		Sunday	
Date		Date		Date		Date		Date		Date		Date	
Seizures Yes / No	Not done	Seizures Yes / No	Not done	Seizures Yes / No	Not done	Seizures Yes / No	Not done	Seizures Yes / No	Not done	Seizures Yes / No	Not done	Seizures Yes / No	Not done
Seizure code	Number of seizures today	Seizure code	Number of seizures today	Seizure code	Number of seizures today	Seizure code	Number of seizures today	Seizure code	Number of seizures today	Seizure code	Number of seizures today	Seizure code	Number of seizures today
Date		Date		Date		Date		Date		Date		Date	
Seizures Yes / No	Not done	Seizures Yes / No	Not done	Seizures Yes / No	Not done	Seizures Yes / No	Not done	Seizures Yes / No	Not done	Seizures Yes / No	Not done	Seizures Yes / No	Not done
Seizure code	Number of seizures today	Seizure code	Number of seizures today	Seizure code	Number of seizures today	Seizure code	Number of seizures today	Seizure code	Number of seizures today	Seizure code	Number of seizures today	Seizure code	Number of seizures today
Date		Date		Date		Date		Date		Date		Date	
Seizures Yes / No	Not done	Seizures Yes / No	Not done	Seizures Yes / No	Not done	Seizures Yes / No	Not done	Seizures Yes / No	Not done	Seizures Yes / No	Not done	Seizures Yes / No	Not done
Seizure code	Number of seizures today	Seizure code	Number of seizures today	Seizure code	Number of seizures today	Seizure code	Number of seizures today	Seizure code	Number of seizures today	Seizure code	Number of seizures today	Seizure code	Number of seizures today
Date		Date		Date		Date		Date		Date		Date	
Seizures Yes / No	Not done	Seizures Yes / No	Not done	Seizures Yes / No	Not done	Seizures Yes / No	Not done	Seizures Yes / No	Not done	Seizures Yes / No	Not done	Seizures Yes / No	Not done
Seizure code	Number of seizures today	Seizure code	Number of seizures today	Seizure code	Number of seizures today	Seizure code	Number of seizures today	Seizure code	Number of seizures today	Seizure code	Number of seizures today	Seizure code	Number of seizures today

Illness, injury or side effects

Please record any illnesses, injuries or side effects you experience during the trial in the table below:

Date	Description of illness, injury or side effect

Changes in seizures

If you notice any changes in you seizures, for example, unusually severe seizures or seizures you do not usually experience, please record this in the table below.

Date	Description of seizure

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PGfAR
PHR

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