Antiepileptic drug management in pregnancy: A double blind randomised trial on effectiveness and acceptability of monitoring strategies (EMPIRE study)

Trial registration: 01253916

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] Alex Pirie,[8] Elaine Denny,[4] Doug McCorry,[5] Khalid S Khan[1,2,3] for EMPiRE Collaborative Network*

[1]Women's Health Research Unit, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, UK

[2]Multidisciplinary Evidence Synthesis Hub (mEsh), Queen Mary University of London, UK

[3]Pragmatic Clinical Trials Unit, Barts and The London School of Medicine and Dentistry, Queen Mary University of London, UK

[4]Centre for Health and Social Care Research, Birmingham City University, UK

[5]Neuropsychiatry Department, The Barberry, Birmingham, UK

[6]Birmingham Children's Hospital, Birmingham, UK

[7]Department of Neurology, Royal London Hospital, London, UK

[8]Birmingham Women's Hospital, Birmingham, UK

[9]School of Clinical and Experimental Medicine, University of Birmingham, UK

[10]Patient and Public Involvement (PPI) group member, Katie's team, Katherine Twining Network, UK

[11]Health Economics Unit, University of Birmingham, UK

[12]Birmingham Clinical Trials Unit, University of Birmingham, UK

[13]Epilepsy Action Charity, Leeds, UK

* See Appendix 3 - List of collaborators

Corresponding author: Shakila Thangaratinam, Professor of Maternal and Perinatal Health, Women's Health Research Unit, Barts and the London School of Medicine and Dentistry. Queen Mary University of London, London. Tel: +44 788777589 E-mail: s.thangaratinam@qmul.ac.uk

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ABSTRACT

Background:

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

Objective:

To determine whether in pregnant women with epilepsy on AEDs, additional therapeutic drug monitoring (TDM) reduces seizure deterioration compared to monitoring based on clinical features alone (CFM) after a fall in serum AED levels.

Design:

A multicentre double blind randomised control trial embedded within a cohort study, alongside a qualitative study. 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.

Participants:

Pregnant women with epilepsy on one or more of the following AEDs: lamotrigine, carbamazepine, phenytoin, levetiracetam. Women with a 25% or more fall in AED level from baseline were randomised to TDM or CFM strategies.

Interventions:

In the TDM arm, clinicians had access to clinical findings and monthly AED levels to guide AED dosage adjustment for seizure control. In the CFM arm, AED dosage adjustment was based on only clinical features.

Outcome:

Primary outcome: Seizure deterioration defined as time to first seizure and to all seizures after randomisation per woman until six weeks postpartum.

Secondary outcome: Pregnancy complications in mother and offspring, maternal quality of life, seizure rates in cohorts with stable AED level, AED dose exposure and adverse events related to AED.

Analysis:

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

Results:

130 women were randomised to TDM,133 to CFM and 294 did not have a fall in AED level. 127 (TDM) and 130 (CFM) (98% complete data) were included in primary analysis. There were no significant differences in time to first seizure (HR 0.82; 95% CI 0.55,1.2), or timing of all seizure after randomisation (HR 1.3, 95% CI 0.70,2.5) between both strategies. Compared to the group with stable AED levels, there were no significant increases in seizures in the CFM (OR 0.93; 95% CI 0.56,1.5) or TDM group (OR 0.93; 95% CI 0.56,1.5) with fall in AED levels. Maternal and neonatal outcomes were similar in both arms, except for higher cord blood levels of lamotrigine (MD 0.55 mg/l; 95% CI 0.11,1), levetiracetam (MD 7.8 mg/l; 95% CI 0.86,14.8) in TDM than CFM 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:

Further evaluation of the risks of seizure deterioration for various threshold levels of fall in AED 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.

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GLOSSARY OF TERMS AND ABBREVIATIONS

AE	Adverse Event
AED	Antiepileptic Drug
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CBZ	Carbamazepine
CFM	Clinical Features Monitoring
CI	Chief Investigator
95% CI	95% Confidence Interval
CRF	Case Report Form
CRO	Contract Research Organisation
DMC	Data Monitoring Committee
EC	European Commission
GCP	Good Clinical Practice
GAfREC	Governance Arrangements for NHS Research Ethics Committees
ICF	Informed Consent Form
ISRCTN	International Standard Randomised Controlled Trial Number
JRO	Joint Research and Development Office
LEV	Levetiracetam
LTG	Lamotrigine
MA	Marketing Authorisation
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator
QA	Quality Assurance
QOL	Quality of Life
QC	Quality Control
Participant	An individual who takes part in a clinical trial
PHT	Phenytoin
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event

SDV	Source Document Verification
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
TCS	Tonic-Clonic Seizure
TDM	Therapeutic Drug Monitoring
TMG	Trial Management Group
TSC	Trial Steering Committee

PLAIN ENGLISH SUMMARY

Pregnant women with epilepsy who take medication for their seizures may have a fall 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 NICE and SIGN guidelines do not recommend this strategy. There is a lack of evidence to support either management.

The 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 561 mothers with epilepsy on medication, the drug levels fell in 267 women. The risk of seizures, pregnancy complications, infant's birth weight and quality of life of mothers were similar in the groups managed by monitoring drug levels regularly or based on only clinical findings. We did not identify an increase in seizures with fall in drug levels. Babies born to mothers with regular monitoring of drug levels were exposed to higher dose of the drug at birth. Women reported that the decisions 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 anti-epileptic drug levels in pregnancy.

Word Count: 250

SCIENTIFIC SUMMARY

BACKGROUND

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

OBJECTIVES

PRIMARY

To determine in pregnant women with epilepsy on AEDs who experience a 25% fall in serum AED levels, whether additional therapeutic drug monitoring (TDM) reduces the risk of seizure deterioration compared to clinical features based monitoring (CFM) alone.

SECONDARY

- To determine if there is a relationship between level of fall 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

We conducted a double blind randomised trial nested within a cohort study, and undertook qualitative study of acceptability of the two strategies.

SETTING

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

PARTICIPANTS

Inclusion criteria

Pregnant women on AED with 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); and capable of understanding English.

Exclusion criteria

Women under 16 years of age; a diagnosis of status epilepticus or non-epileptic seizures; 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; or 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, birth weight, head circumference, cord blood AED levels.

STUDY CONDUCT

Women with epilepsy on AED recruited in the study cohort were randomised to TDM or CFM strategy, if there was a 25 percent or more fall in serum AED levels at any time in pregnancy, compared to baseline or pre-pregnancy levels. Women and clinicians in the CFM 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 reduction (hazard ratio~0.75) with TDM, providing 80% power (at p=0.05), assuming an outcome-free survival rate of 60% in the CFM group and 10% loss to follow up.

ANALYSIS

All analyses were on 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. Multivariate failure time analysis of time to first, and to 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 Anderson-Gill model.

RESULTS

We recruited 561 mothers from 50 hospitals, randomised 267 to either TDM or CFM arms, and included data from 257 women for primary analysis. There were no significant differences between the two arms for time to first seizure (HR 0.82 95% CI 0.55, 1.2), or time to multiple seizures (HR 1.34; 95% CI 0.70, 2.6). There were no differences in maternal and fetal complications, breast-feeding, birth weight, cord pH, and quality of life in both arms. The cord blood levels of lamotrigine and levetiracetam were higher in TDM than CFM groups with adjusted mean differences of 0.55 mg/l (95% CI 0.11, 1.0) and 7.8 mg/l (95% CI 0.86, 14.8) respectively, with similar levels of carbamazepine between the groups.

Compared to the non-randomised group with stable serum AED levels, there were no significant increases in seizures in the CFM (OR 0.93; 95% CI 0.56,1.5) or TDM group (OR 0.93; 95% CI 0.56,1.5). Increase in exposure to AED dose in women on monotherapy and polytherapy had no significant effect on maternal and neonatal outcomes, except for increase in cord blood levels of lamotrigine MD 0.55 mg/l (95% CI 0.11, 1.0) and levetiracetam MD 7.8mg/l (95% CI 0.86, 14.8) in TDM than CFM group. There were no differences for cord blood levels of carbamazepine (MD -0.47mg/l, 95% CI 1.5, 0.6) 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 concerns for their babies born without any health problems.

CONCLUSIONS

There is 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. Although there are no increase in short term maternal or fetal complications with drug monitoring strategy than clinical based one, the long term neurodevelopment of babies exposed to higher serum AED levels in this group needs further evaluation.

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CHAPTER 1 INTRODUCTION

1.1 BURDEN OF THE PROBLEM

Epilepsy complicates 0.6% of all pregnancies in the UK affects 0.5-1% of the general population.[1] Approximately one-third of people receiving anti-epileptic drugs (AED) are of reproductive age [2] and there is a rise in the number of pregnancies exposed to AEDs in the past few decades. The maternal mortality among pregnant women with epilepsy is 10-fold higher than the mortality rate in women without epilepsy.[1] In 2009-2012, 14 maternal deaths in the UK were attributed to epilepsy [3] and SUDEP (Sudden Unexpected Death in Epilepsy) accounting for about 80% of deaths in women with epilepsy.[1, 3] 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.[3, 4]

In addition to major risks to the mother, uncontrolled epilepsy with generalised tonic-clonic convulsions carries risk of harm to fetus including miscarriage, fetal hypoxia and acidosis and fetal loss.[5-7] Effect of epilepsy tends into daily living resulting in loss of driving license, 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.

AED exposure in-utero is associated with congenital malformation.[8] with fetal risk related to the number of AEDs, AED type and probably AED dose.[9] Furthermore, the magnitude of AED dose exposure to the fetus in-utero, and the continuation of AED intake in pregnancy on long-term neurological development of children are not known. There is a general consensus that the risks of uncontrolled convulsive seizures in the mother outweigh the potential teratogenic risk and any other adverse effect on the offspring.[10, 11]

AED levels fall in pregnancy in a proportion of women with epilepsy, and are hypothesised to aggravate seizures.[12-14] Monitoring of serum AED levels in each trimester and after delivery has been recommended by American Academy of Neurology based on consensus as a good practice.[15] In the UK however, the NICE (National Institute for Health and Clinical Excellence) and SIGN (Scottish Intercollegiate Guidelines Network) guidelines do not recommend regular AED monitoring in pregnancy due to a paucity of evidence.[11]

There are no randomised trials evaluating the effects of additional therapeutic monitoring (TDM) over management based on clinical features (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 quality of life of the mother and pregnancy outcomes is not known.

1.2 OBJECTIVES

PRIMARY OBJECTIVE

To determine in pregnant women with epilepsy on anti-epileptic drugs (AED) who experience a 25% fall from baseline in serum AED levels, whether a strategy of additional therapeutic drug monitoring (TDM) compared to clinical features monitoring (CFM) alone to determine optimal dose of AED reduces the risk of seizures.

SECONDARY OBJECTIVES

1. To determine if there is a relationship between level of fall in serum AED levels and seizures, by comparing women in non-randomised cohort with stable levels, with those in randomised cohorts with fall in levels.
2. To evaluate the effect of the two monitoring strategies on maternal and fetal outcomes in women with fall in serum AED levels.
3. To assess the effect of TDM vs. CFM on quality of life in pregnant women with epilepsy on AEDs.
4. To identify any differences in total AED dose exposure between TDM and CFM strategies.
5. To assess the adverse effects of AED 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 AED in the context of their lives through qualitative study
7. To evaluate the cost effectiveness of the two strategies

CHAPTER 2 METHODS

2.1 STUDY DESIGN

Randomised trial embedded within a cohort study with a qualitative study. The study received ethical approval from the NRES Committee West Midlands (11/WM/0164), trial registration 01253916.

2.2 SETTING

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

2.3 PATIENT AND PUBLIC INVOLVEMENT

The Epilepsy Action charity assisted with the trial design and promotion. A member of the charity (AP) contributed in steering committee meetings to the general management of the project.

A patient representative (NgM) sat on the trial management and trial steering committee panels and provided input towards the overall supervision of the trial

2.3 ELIGIBILITY CRITERIA

For inclusion in the trial, participants fulfilled the following eligibility criteria;
Inclusion criteria

- Viable pregnancy of less than 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:

- Less than 16 years of age
- Documented status epilepticus in the last year or non-epileptic seizures in the last two years
- Non-LTG polytherapy or Sodium Valproate (VPA) 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 two years
- Expressed an intention not to take AED in pregnancy

2.4 HEALTH TECHNOLOGIES ASSESSED

Women with a fall in serum AED levels in pregnancy compared to 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 (TDM) 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 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 (CFM) 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 responsible clinician based on clinical features alone.

2.5 RANDOMISATION

Participants were allocated in 1:1 ratio to TDM or CFM using a stratified block randomisation with random block size of two, four or six to decrease predictability. Stratification variables were:

- Baseline AED therapy: 1) Lamotrigine monotherapy, 2) carbamazepine, phenytoin or levetiracetam monotherapy or 3) lamotrigine polytherapy
- 1) Presence or 2) absence of seizures three months prior to pregnancy

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

2.6 OUTCOME

2.6.1 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 six weeks post-delivery.

2.6.2 SECONDARY OUTCOMES

Maternal:

Neurological: Proportion of women experiencing seizures who were seizure-free in three month prior to consent, number of seizures per week and number of seizure-free days per week, mean daily AED dose exposure, adverse events as measured by the Liverpool Adverse Events Profile.

Obstetric: maternal death, mode of delivery, preterm labour, induction of labour, pre-eclampsia, antepartum and postpartum haemorrhage, admission to high dependency/intensive care unit, breast feeding, infection, gestational diabetes mellitus.

Quality of Life: Epilepsy specific QoL as measured by QOLIE-31, generic QoL as measured by 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, [16] minor abnormalities, Apgar scores at 1' and 5', admission to neonatal unit, birth weight, head circumference, fetal growth, cord blood levels of AED.

2.7 STUDY CONDUCT

Relevant neurological and obstetric history 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 six months, seizure types, epilepsy syndrome, aetiology of epilepsy, duration of epilepsy, current AED and dose, baseline serum AED level, indications of depression (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 Neurological Disorders Depression

Inventory for Epilepsy (NDDI-E). A score over 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 in monthly intervals until 6-8weeks postpartum. Women were asked to record seizure activity in diaries specially developed for collecting trial data throughout the course of their participation. Women completed EQ-5D (maximum score 1), Liverpool Adverse Events Profile (maximum score 76) and Patient Costs questionnaire at baseline, all follow up and post-natal visits. Responses to QOLIE-31 (maximum score 100 or QOLIE-31 overall health, maximum score 10) were collected at baseline and in late pregnancy (32-36 weeks gestation). A higher score indicates a better health state.

Women with a 25 percent or more fall in serum AED levels at any time in pregnancy, compared to baseline, or pre-pregnancy levels, were randomised to TDM or CFM. Women without a fall in serum AED levels continued to be monitored in the non-randomised arm, and were randomised if their AED levels fell below 25 percent at any time until delivery. Women and clinicians in CFM arm and non-randomised cohort were blinded to the results. If randomised to the TDM arm, the serum levels were communicated to the participating centre within one 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 seven 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, bloods 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 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 4.

The study has been reported in line with recommended guidelines.[17, 18]

2.8 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.

2.9 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.

2.10 SAMPLE SIZE ESTIMATION

A large prospective registry of pregnant women with epilepsy suggested that around 40% of women experience seizures during pregnancy.[19] We set the outcome-free survival rate under CFM 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.

Table 1: Sample size estimates for different powers and effects sizes

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

We aimed to collect data from at least 594 randomised women, giving 80% power (at p=0.05) to detect a 25% seizure hazard reduction (hazard ratio~0.75). We considered 25% to be 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 fall in serum AED level.

2.11 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 and P-values. All analyses were carried out using Stata version 12.0.

The primary analysis of time to first seizure was performed using a Cox proportional hazard model. The primary multivariate failure time analysis of time to first seizure, 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, the Anderson-Gill model.[20] 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 three month 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 (TCS / non-TCS / unclassified).

Secondary analyses of differences between the two randomised arms for pregnancy outcomes, cord blood AED levels, and quality of life were performed using analysis of covariance. We used Poisson models for analyses of LAEP, logistic models for binary

outcomes, ordered logistic regression for categorical outcome breastfeeding and linear regression for continuous outcomes.

We analysed the association between fall in serum AED levels and seizure status using logistic regression models for the binary outcome of seizure free status by 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 CFM and the non -randomised cohort. AED dose exposure was compared between TDM, CFM and non-randomised cohort using linear regression. For analysis of participants on multiple AEDs we used multivariate multiple regression to analysis 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 by using a simpler ANCOVA 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.

2.11.1 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 Wald test for treatment-covariate interactions. We investigated whether any treatment effect differed by seizure type by only considering tonic-clonic seizures as outcomes.

2.11.2 MISSING VALUES

Withdrawals and those lost to follow up were included in the analysis up to the last point that data is 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, they were reviewed by two independent neurologists (DM, 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, a third neurologist (SS) was sought. When all neurologists were unable to provide estimation on likelihood of seizure, the average seizure rate for tonic clonic seizures (TCS) and the rate for non-TCS 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 was available, the average rate over any seizure type was used. If multiple seizures occurred during a timeframe they were equally spaced out over the timeframe. If the number of seizures was larger than the number of days, the seizures were equally spaced out over each day in the timeframe. A sensitivity analysis was conducted for the analysis of time to first seizure to investigate whether an interval censoring approach showed a different result. When there was missing data on seizure occurrence, participants were censored at the first date where seizure occurrence was known. A sensitivity analysis will be performed for the analysis of multiple events ignoring any dates or date ranges where seizure occurrence is unknown.

2.11.3 SENSITIVITY ANALYSIS FOR INTERVAL ANALYSIS FOR TIME TO FIRST SEIZURE

This sensitivity analysis was planned a priori but not conducted. The reason 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, since 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 only allow one event to occur during the period of uncertainty. Allowing for multiple events during the period of uncertainty would require the applications of multistate models would likely 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, due to the small number and the issues arising for other women as described in the previous paragraph, it was decided not to perform this analysis.

2.11.4 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 3 independent members in the 5-member DMC. The terms of reference and charter for the DMC were determined at the outset taking into account issues relevant to monitoring of this study.[21]

2.11.5 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 the planned sample size was not recruited, it was postponed pending results to see whether 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

3.1 FLOW OF WOMEN RECRUITED IN THE STUDY

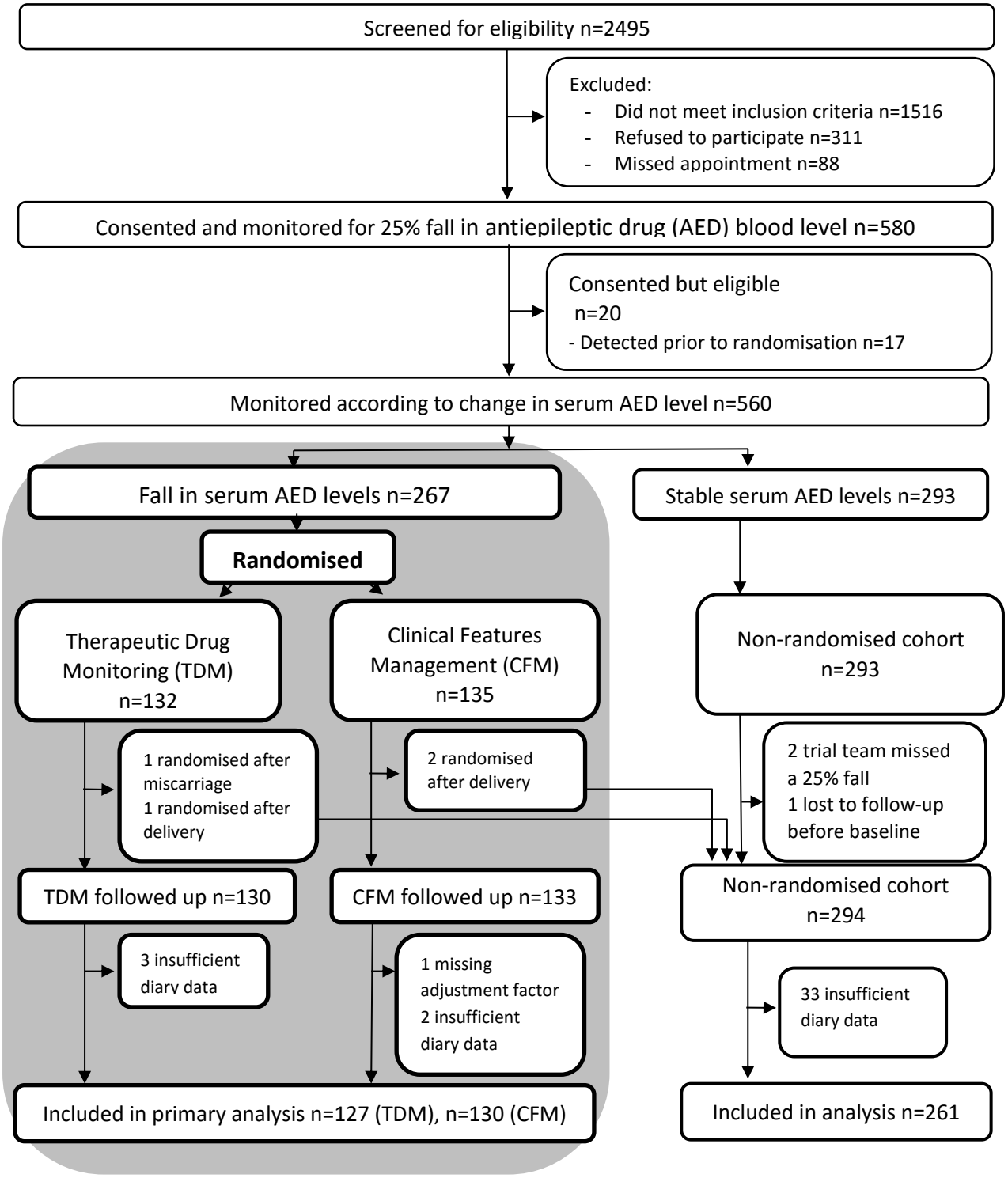

Figure 1: CONSORT flow chart

We recruited 593 women; 580 for the cohort, and 13 for the qualitative study. The median number of women recruited per centre was 9 (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 fall 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 fall in serum AED level at some point in pregnancy, and were randomised to TDM (n=130) or CFM (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 primary analysis was available from 127 women (98%) in TDM group, 130 (98%) in CFM and 294 (99%) in non-randomised group (*Figure 1*).

3.2 CHARACTERISTICS OF WOMEN INCLUDED

85% of recruited women in TDM, CFM and non-randomised groups were white. Around 60% in each of the groups had completed A levels or higher in their education. Half of all women in non-randomised cohort (50%) were nulliparous, and the corresponding figures were 58% and 54% in TDM and CFM groups respectively. The rates of congenital abnormalities in previous pregnancies were between 5 and 8% of women in TDM, CFM and non-randomised groups. There was a history of mental illness in about a tenth of women (*Table 2*).

Tonic clonic seizure was the most commonly diagnosed type of seizure in 80% (100/130) of women in TDM, 82% (109/133) in CFM, and 81% (237/294) in non-randomised cohort. A quarter of women in each of the randomised groups TDM (26%, 34/130) and CFM (24% 32/133), and a third in the non-randomised group (29%, 84/294) were seizure free for 3 months before pregnancy. Lamotrigine (LTG) monotherapy was the most common AED medication taken by around half of the women baseline. LTG polytherapy was taken by a tenth in TDM (11%, 14/130) and CFM (9%, 12/133) groups, and by 5% in non-randomised cohort (15/294). The dose of individual AEDs taken at the time of randomisation in TDM and CFM groups are provided in Table 2.

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

Variable	N (TDM), N (CFM), N (NR)	Randomised group		Non-randomised (NR) N (%)
		Therapeutic Drug Monitoring (TDM) N (%)	Clinical Features Monitoring (CFM), N (%)	
Total number of women		130	133	294
Demographics				
Ethnic group	130,133,294			
- 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	127,133,292			
- Degree Level		50 (39%)	49 (37%)	114 (39%)
- A Level		29 (23%)	33 (25%)	68 (23%)
- GCSE Level		44 (35%)	48 (36%)	87 (30%)
- Below GCSE Level		4 (3%)	3 (2%)	23 (8%)
Smoking status	130,133,294			
- 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	130,133,294			
- 0 units		122 (94%)	117 (88%)	266 (91%)
- 1 to 9 units		8 (6%)	16 (12%)	25 (9%)
- 10+ units		0 (0 %)	0 (0%)	3 (1%)
Obstetric history				
Parity	130,133,294			
- 0		75 (58%)	72 (54%)	147 (50%)
- 1-4		55 (42%)	59 (44%)	144 (49%)
- 5+		0 (0%)	2 (2%)	3 (1%)
Previous children				
Neonatal deaths, N(%)	76,100,225	1 (1%)	1 (1%)	2 (1%)
Stillbirths, N(%)	76,100,226	0 (0%)	0 (0%)	3 (1%)
At least 1 congenital abnormality in previous children, N(%)	76,100,225	7 (7%)	4 (5%)	17 (8%)

Medical history							
Maternal congenital abnormalities	130,133,293	5	(4%)	5	(4%)	5	(2%)
Diabetes	130,133,293	3	(2%)	1	(1%)	9	(3%)
Chronic Hypertension	130,133,293	2	(2%)	2	(2%)	7	(2%)
Renal disease	130,133,293	3	(2%)	2	(2%)	5	(2%)
HIV	130,133,293	0	(0%)	0	(0%)	1	(0%)
Learning difficulties	129,133,292	3	(2%)	1	(1%)	11	(4%)
Mental Illness	130,133,293	19	(15%)	15	(11%)	33	(11%)

Table 3: Baseline neurological characteristics of women in the study

Variable	N (TDM), N (CFM), N (NR)	Randomised group		Non-randomised cohort	
		Therapeutic Drug Monitoring (TDM) N (%)		Clinical Features Monitoring (CFM), N (%)	
Age at first seizure (y) Mean (SD)	130,132,290	16.8	(8)	17.0	(7)	16.1	(7)
Years since first seizure (y) Mean (SD)	121,124,261	12.2	(8)	12.1	(7)	16.1	(8)
Seizures 3 months prior to pregnancy	130,133,294	34.0	(26%)	32.0	(24%)	84.0	(29%)
Seizure classification †	130,133,294						
Tonic-clonic		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							
- LTG monotherapy	130,133,294	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							
	130,133,294						
- Carbamazepine (CBZ)		16	(12%)	20	(15%)	54	(18%)
- Lamotrigine (LTG)		68	(52%)	70	(53%)	148	(50%)
- Levetiracetam (LEV)		31	(24%)	31	(23%)	77	(26%)
- Phenytoin (PHY)		1	(1%)	0	(0%)	0	(0%)
- Lamotrigine & Levetiracetam		14	(11%)	11	(8%)	15	(5%)

- Lamotrigine & Carbamazepine		0	(0%)	1	(1%)	0	(0%)
Dose of AED at randomisation (mean, SD) mg							
CBZ only	16,20	581.3	(339.1)	695.0	(336.4)		
LTG only	6870	246.3	(124.4)	242.9	(148.5)		
LEV only	31,31	1500.0	(724.6)	1572.6	(880.8)		
PHY only	0,1			200.0			
LTG&LEV, LTG dose	14,11	448.2	(215.8)	379.6	(92.8)		
LTG&LEV, LEV dose	14,10	1767.9	(846.2)	2100.0	(1119.3)		
LTG&CBZ, LTG dose	0,1			200.0			
LTG&CBZ, CBZ dose	0,1			300.0			

† Some women experience more than 1 seizure type

Baseline quality of life measurements are provided in Table 4. Scores for Neurological Disorders Depression Inventory in Epilepsy (NDDI-E), Quality of life (EQ-5D), Liverpool Adverse Events Profile (LAEP) and Quality of Life in Epilepsy Inventory (QOLIE-31) were balanced across TDM and CFM groups.

Table 4: Baseline scores for questionnaires

Variable	**N (TDM), N (CFM), N (NR)**	**Randomised Group**				**Non-randomised cohort**	
		Therapeutic Drug Monitoring (TDM) Mean (SD)		**Clinical Features Monitoring (CFM) Mean (SD)**		**Mean (SD)**	
Number of women		130		133		294	
NDDI-E[1]	130,133,284	9.7	(3.3)	9.9	(3.6)	10.1	(3.5)
EQ-5D[2]	126,127,267	0.90	(0.17)	0.90	(0.16)	0.89	(0.18)
LAEP[3]	124,121,259	34.3	(8.9)	34.9	(10.4)	35.3	(9.2)
QOLIE-31 score[4] (UK)	128,128,274	73.7	(14.6)	72.8	(15.5)	71.0	(16.8)
QOLIE-31 overall health[5] (UK)	127,128,273	7.0	(1.8)	7.0	(1.9)	7.1	(1.8)

[1] Neurologic Disorders Depression Inventory in Epilepsy (maximum score 24)
[2] Euro Quality of Life five dimensions questionnaire (maximum score 1)
[3] The Liverpool Adverse Events Profile (maximum score 76)
[4] Quality of Life in Epilepsy Inventory- 31(maximum score 100)
[5] Quality of Life in Epilepsy Inventory- 31 for overall health (maximum score 10)

3.3 TIME TO RANDOMISATION FROM CONSENT

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

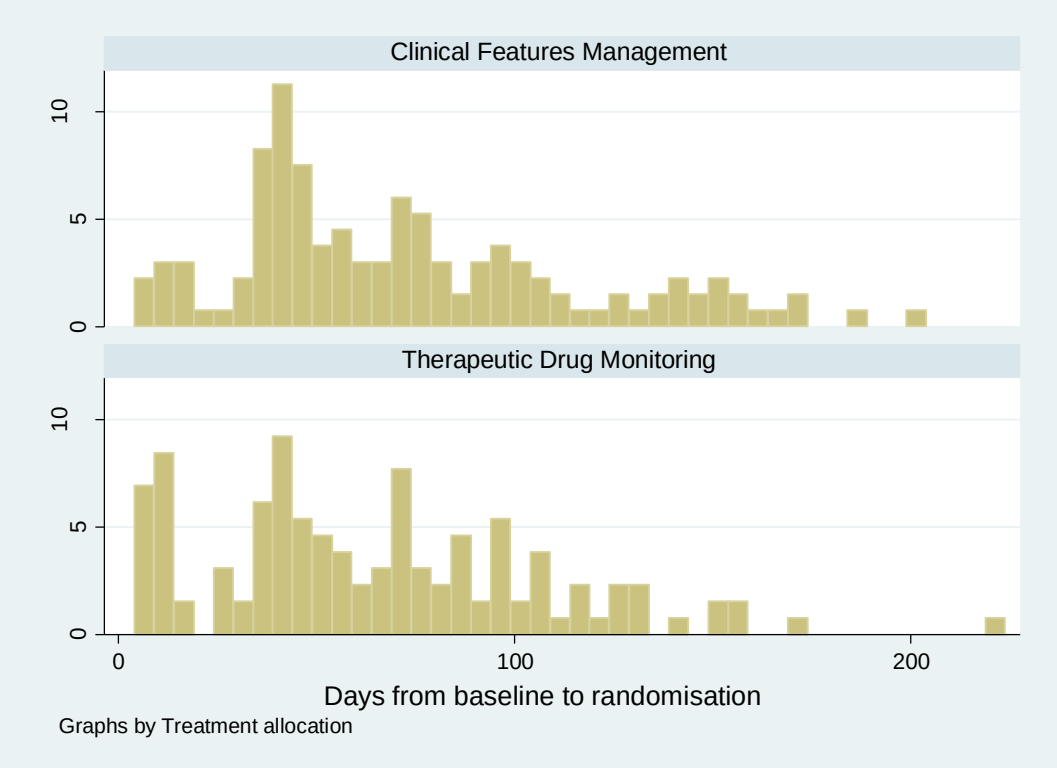

Figure 2: Time from baseline to randomisation in days

3.4 EFFECTS OF TDM AND CFM STRATEGIES FOR AED DOSING ON MATERNAL SEIZURES

257 women provided a cumulative analysis time of 35859 days from randomisation to censoring, with 25001 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 TDM and CFM groups, respectively. The number of days with seizure, and actual number of seizures occurred in both groups are provided in Table 5 below.

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

Variable	N(TDM), N(CFM)	Randomised group	
		Therapeutic Drug Monitoring (TDM)	Clinical Features Monitoring (CFM)
Total observation period	**127,130**		
- less than 12 weeks		11 (8%)	32 (25%)
- 12 to less than 24 weeks		69 (54%)	65 (50%)
- 24 to less than 36 weeks		46 (36%)	32 (25%)
- 36 or more weeks		1 (1%)	1 (1%)
Median(IQR) in days		153 (115-179)	134 (84-169)
Number of days with any seizures	**127,130**		
- None		79 (66%)	80 (63%)
- 1 to 29		36 (30%)	43 (34%)
- 30 to 59		5 (4%)	2 (2%)
- 60 to 89		0 (0%)	2 (2%)
- 90 or more		7 (6%)	3 (2%)
Median(IQR)		0 (0-3)	0 (0-4)
Total number of seizures	**127,130**		
- No seizures		79 (64%)	80 (62%)
- 1 to 9		29 (24%)	26 (20%)
- 10 to 99		10 (8%)	20 (16%)
- 100 to 499		6 (5%)	3 (2%)
- 500 or more		3 (2%)	1 (1%)
Median(IQR)		0 (0-4)	0 (0-5)

Seizure data was captured from randomisation to the first day of missing data. A quarter of women in CFM had a total observation period of less than 12 weeks in comparison to 8% of TDM. A total observation period of 12 to 24 weeks was seen in half of each randomised group and a quarter of CFM and a third of TDM had a total observation period of 24 to 36 weeks. One women in each group had seizure data captured for more than 36 weeks. The mean number of days with captured seizure data was higher for TDM by 19 days.

Two thirds of each randomised group did not experience any seizures after randomisation whereas approximately a third of both groups experienced 1-29 days with seizures. Less than

a quarter of both groups had up to 9 seizures post-randomisation. Double the number of women experienced 10-99 seizures in CFM (16%) in comparison to TDM (8%). Small numbers of women in each group experienced more than 100 seizures after randomisation and 30 or more days of seizures.

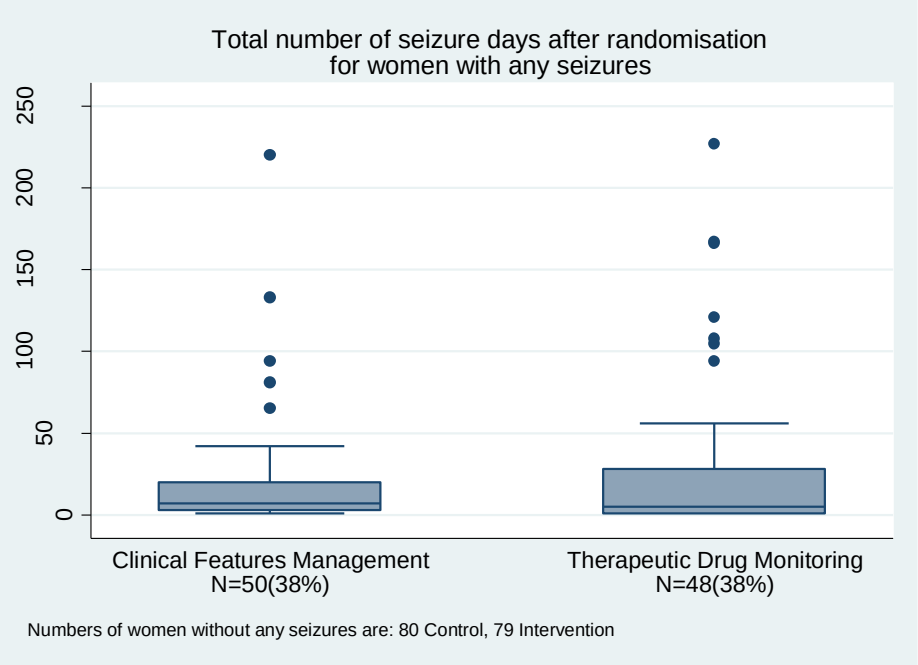

Figure 3: Seizure diaries - Total number of days with any seizures from randomisation to end of follow-up by allocation group excluding women with no seizures

There were no differences in the proportion of women who experienced at least one seizure in the TDM (48/127, 38%) and CFM (50/130, 38%) groups, with mean observed time to first seizure of 28 (SD 42) days in TDM and 27 (SD 36) days in CFM group. There was a 20% reduction in time to first seizure with TDM than CFM, which was not significant (HR 0.8, 95% CI 0.55, 1.2). The confidence interval suggest a possible effect of between 45% decrease and 20% increase in seizure rate with TDM and includes a hazard ratio of 0.75; therefore possibility of a clinically relevant difference between TDM and CFM 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 confidence interval but not the effect size or statistical significance (HR

0.8, 95% CI 0.54, 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 3year 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.

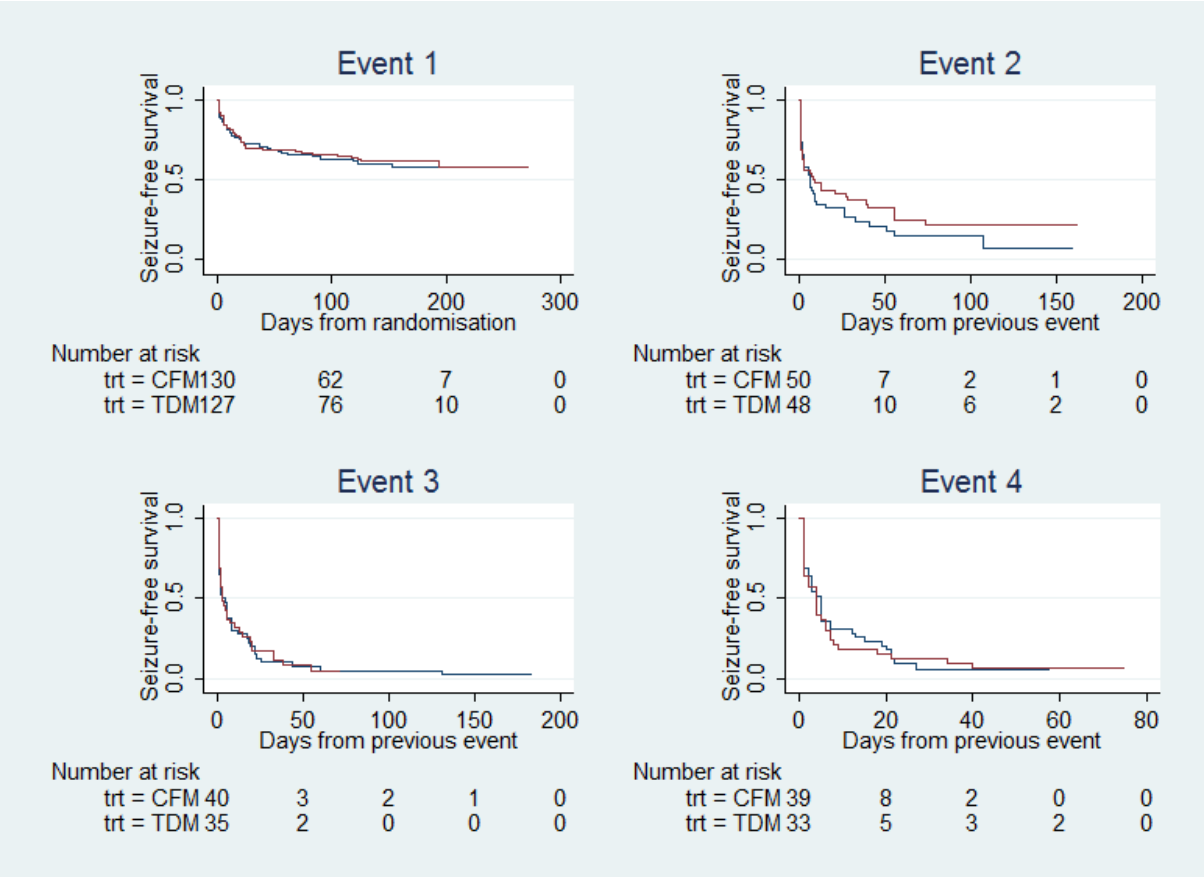

Figure 4: Survival graphs for time to first seizure and time to subsequent seizures after randomisation

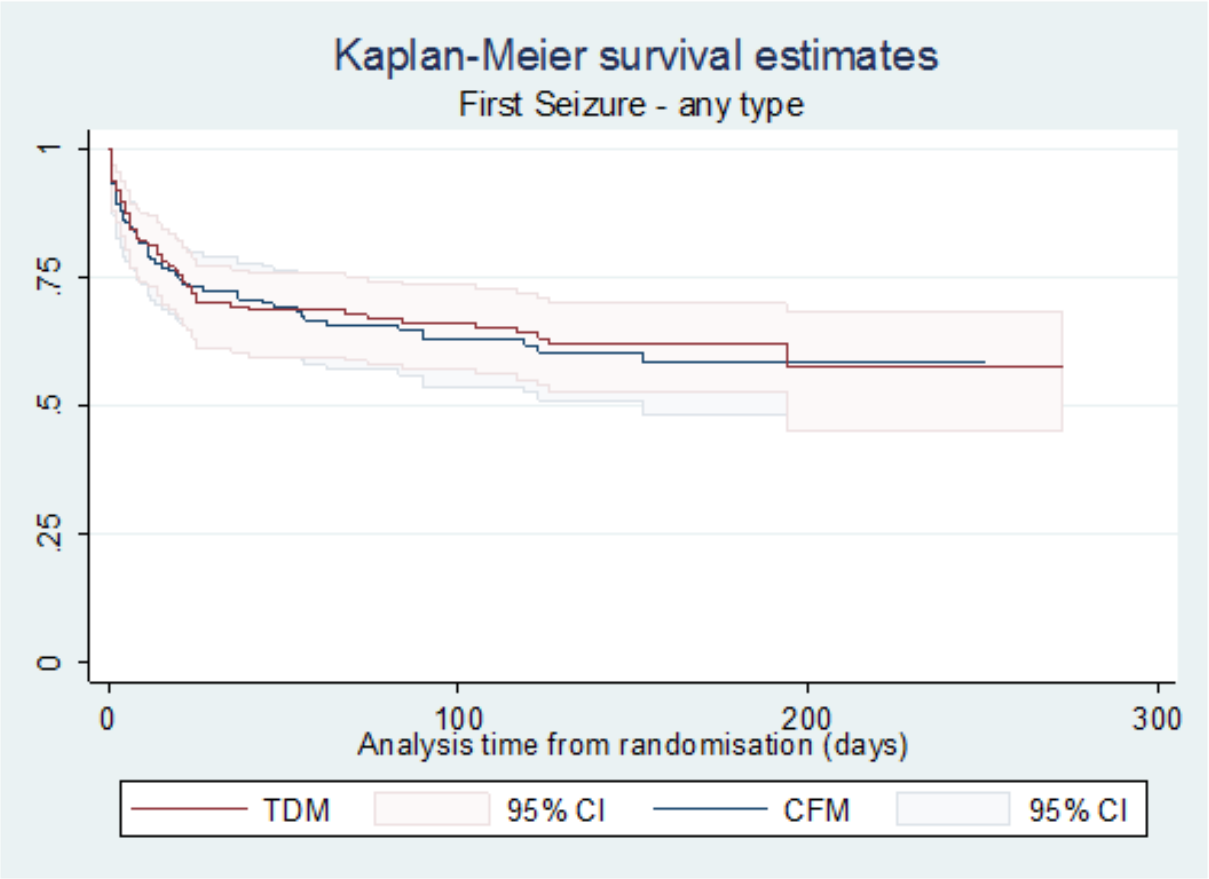

Figure 5: Survival graph of time to first seizure

Ninety eight (38%) women experienced only one seizure, 75 (29%) 2 or more, 72 (28%) 3 or more seizures. Of the 98 women who had suffered the first seizure, 75 women experienced the second seizure, 35 in TDM and 40 in CFM groups, with mean duration to second seizure of 12.1 and 11.6 days respectively. Subsequently, 72 women with a second seizure had a third seizure, with 33 in TDM (median 3 days, IQR 1, 17)) and 39 CFM (median 3 days, IQR 1, 13) groups.

The analysis of overall time to first and subsequent seizure showed an increase with TDM than CFM, which was not significant (HR 1.3, 95% CI 0.70, 2.6).

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 confidence interval with no changes to statistical significance (HR 1.4, 95% CI 0.73, 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.

3.4.1 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 (*Table 6*).

Table 6: Assumption check - Primary analysis within subgroups of covariates

Covariate	Subgroup	N	Subgroup TDM effect, Hazard Ratio, 95%CI
Seizures 3mths prior	No	192	1.0 (0.35,2.8)
to pregnancy	Yes	65	1.4 (0.68,2.8)
	LTG[1] monotherapy	133	1.1 (0.41,3.0)
Baseline AED group	CBZ[2], PHT[3] or LEV[4] monotherapy	99	1.5 (0.56,4.1)
	LTG polytherapy	25	1.3 (0.27,6.3)
	<25 years	50	1.0 (0.35,2.9)
Maternal age*	25 to <35 years	166	1.8 (0.68,4.6)
	35+ years	41	1.1 (0.21,5.5)
	<10 years	37	0.28 (0.07,1.1)
Age at first seizure*	10 to <20 years	138	1.9 (0.90,4.2)
	20+ years	82	3.3 (0.91,12.1)
	TCS	96	0.40 (0.11,1.4)
Baseline broad	Non-TCS[5]	154	1.4 (0.71,2.8)
seizure classification	Unspecified only	7	0.7 (,)

[1]Lamotrigine
[2]Carbamazepine
[3]Levetiracetam
[4]Phenytoin
[5]Tonic Clonic
* Maternal age and age at first seizure were grouped into clinically meaningful categories for presenting subgroup effects. However, tests for interaction were done on the continuous covariate.

3.4.2 SENSITIVITY ANALYSIS

We undertook 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 31572 days from randomisation to first seizure or censoring. The risk of time to first seizure was lower in women in TDM than CFM group, but this was not statistically significant (HR 0.80, 95%CI 0.43, 1.5).

Table 7: Sensitivity analysis: first event for TCS only

	N	Analysis time in days, Mean (SD)		Proportion of women with any seizures		TDM effect, Hazard Ratio, 95%CI
		TDM	CFM	TDM	CFM	
Time to first tonic-clonic seizure	257	132 (63)	114 (65)	0.16	0.17	0.80 (0.43,1.5)

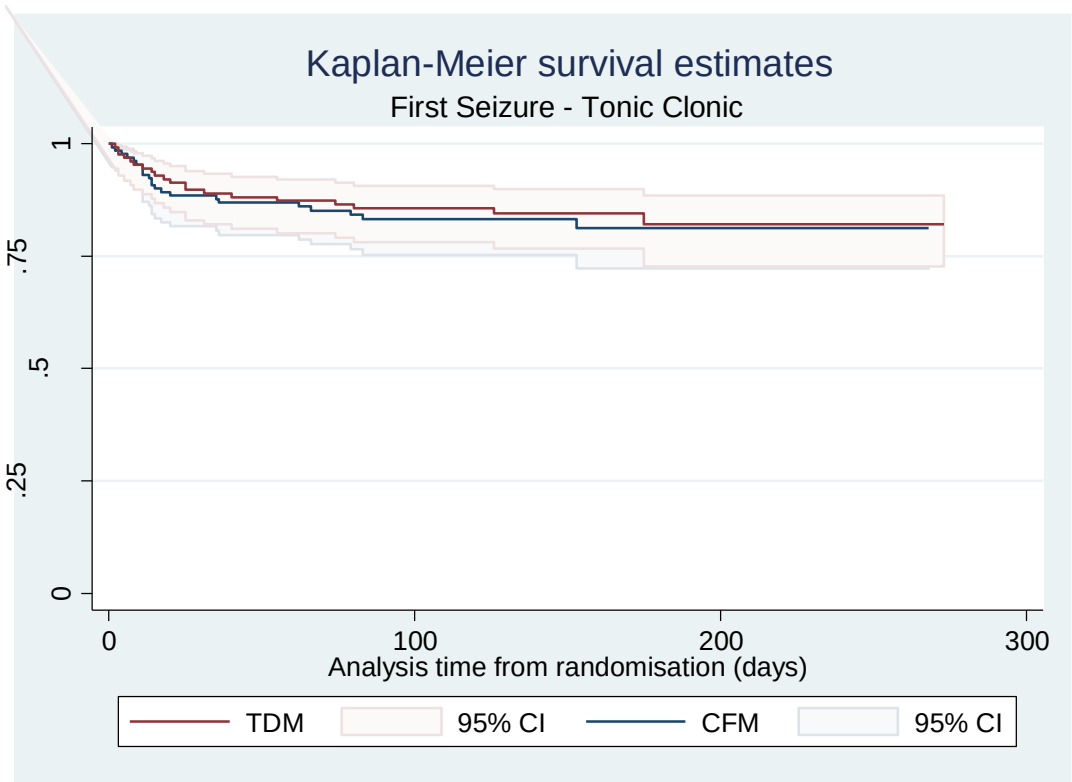

Figure 6: Survival graph for time to first event analysis on TCS only

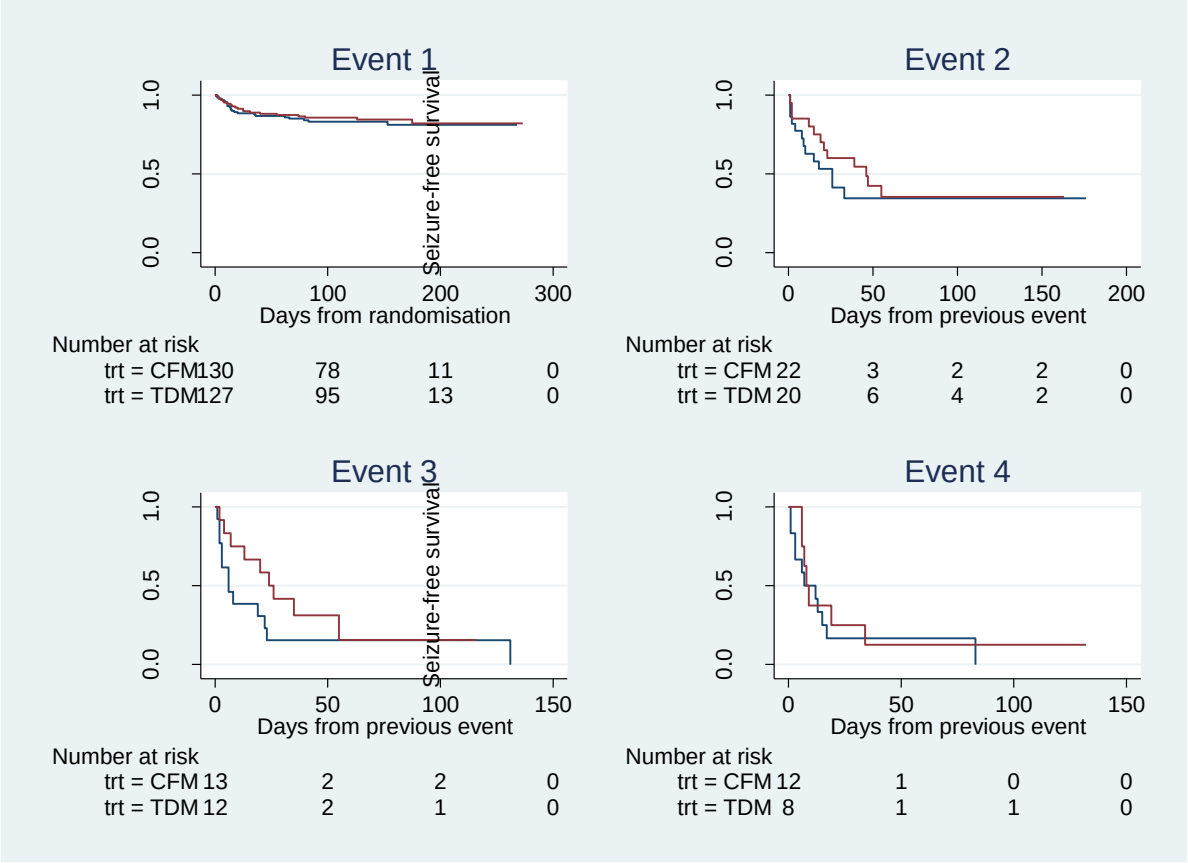

Figure 7: Survival graphs for time to first tonic clonic seizure and time to subsequent tonic clonic seizures

Table 8: Sensitivity analysis: multiple failure times on TCS only

	N	Analysis time in days, Mean (SD)		Number of seizure days, Mean (SD)		TDM effect, Hazard Ratio, 95%CI
		TDM	CFM	TDM	CFM	
Multiple seizure rate	257	149 (50)	130 (55)	0.54 (1.9)	0.84 (3.2)	0.621 (0.28,1.4)

3.5 EFFECTS OF MONITORING STRATEGIES ON MATERNAL AND FETAL OUTCOMES

3.5.1 MATERNAL OUTCOMES

Pregnancy outcomes

There were no differences in gestational age at delivery, preterm birth, mode of delivery, ante or postpartum haemorrhage, admission to neonatal unit or rates of breast feeding between women in TDM or CFM groups (*Table 9*).

Table 9: Effect of AED monitoring strategies on maternal outcomes

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

MD – Mean difference, OR – Odds ratio

Maternal exposure to AED and rates of seizures

Table 10: Differences in dose of AED exposure between the TDM and CFM monitoring strategies

AED	N(TDM), N(CFM)	Mean daily AED[1] exposure in mg (SD)		TDM effect, Mean difference, 95%CI
		Therapeutic Drug Monitoring (TDM)	Clinical Features Monitoring (CFM)	
CBZ[2] only	16, 20	616.7 (355.8)	695.0 (336.4)	-12.1 (-226.7, 202.4)
LTG[3] only	68,70	290.9 (137.5)	252.6 (148.0)	32.3 (-14.4, 79.0)
LEV[4] only	31,31	1735.6 (701.9)	1628.5 (926.5)	166.5 (-229.8, 562.7)
LTG & LEV	11,14	LTG: 487.5 (206.7) LEV: 1920.1 (858.9)	LTG: 413.8 (91.1) LEV:2122.2 (1077.5)	LTG: 97.4 (-28.7, 223.4) LEV: -137.3 (-945.9, 671.4])

[1]Antiepileptic Drugs
[2]Carbamazepine
[3]Lamotrigine
[4]Levetiracetam
[5]Phenytoin

One woman received phenytoin monotherapy and one woman received lamotrigine polytherapy with carbamazepine. No one received phenytoin monotherapy. There were no differences in the mean dose of AED prescribed daily to women in TDM and CFM groups for AEDs provided as monotherapy or as polytherapy (*Table 10*). Appendix 6 shows the effect of increasing the dose of AEDs in women taking monotherapy and polytherapy and found no significant effect on maternal pregnancy outcomes.

3.5.2 FETAL OUTCOMES

There were no neonatal deaths in any of the randomised women and two stillbirths in the CFM group. The odds of major congenital malformations, small for gestational age foetus, and admission to neonatal unit were not different between the two groups (*Table 11*). We did not observe any differences in birth weight, head circumference, Apgar scores at 1 and 5 minutes and cord arterial and venous pH of infants born to mothers exposed to TDM or CFM strategies. The cord blood levels of the AEDs were available for lamotrigine (n=131), carbamazepine (n=26) and levetiracetam (n=66) babies. We observed a significant increase in the cord blood levels of lamotrigine (MD 0.55 mg/L 95% CI 0.11,1.0) and levetiracetam (MD 7.8 mg/L, 95% CI 0.86,14.8) in infants born to mothers managed in the TDM group compared to CFM group. There were no differences for cord blood levels of carbamazepine (MD -0.47, 95% CI 1.5, 0.60) in the two groups. We quantified the effect of increase in AED

dose on fetal outcomes in Appendix 7. 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 7*), levetiracetam by 0.008mg/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 mg/L and 0.008 mg/L for every 1 mg increase in dose of AED in women on polytherapy. The cord blood venous pH was significantly decreased 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 7*).

Table 11: Effect of AED monitoring strategies on fetal outcomes

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

3.5.3 MATERNAL QUALITY OF LIFE

Table 11 compares the quality of life 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, 0.05). The scores for QOLIE-31 and the overall health score were similar between the two groups (*Table 12*).

Table 12: Effects of TDM and CFM strategies on maternal quality of life

Outcome	N(TDM), N(CFM)	Randomised Group		Mean difference** 95%CI
		Therapeutic Drug Monitoring (TDM)	Clinical Features Monitoring (CFM)	
		Mean (SD)	Mean (SD)	
EQ-5D Score	99, 102	0.90 (0.20)	0.90 (0.18)	0.00 (-0.05,0.05)
QOLIE-31 score (UK)	114, 110	71.0 (16.0)	73.7 (13.5)	-2.5 (-5.1,0.0)
QOLIE-31 overall health (UK)	115, 110	6.9 (1.8)	7.3 (1.6)	-0.35 (-0.72,0.02)

** Models are adjusted for baseline values in addition to adjustment factors included in all models

3.5.4 EFFECT OF FALL IN SERUM AED 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 CFM and TDM groups with a fall in serum AED levels more than 25%. There were no significant differences between the groups in seizure status, which was adjusted for baseline seizures in three months prior to pregnancy.

Table 13: Seizure status by end of follow-up compared to baseline

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

There were no differences in the average number of seizures per week, and average number of days with seizures per week, analysed using Poisson models. We removed an extreme outlier with an average of 256 seizures per week.

Table 14: Comparison of average seizure frequency between CFM and non randomised participants

		Median (IQR)		
Outcome	**N**	**Clinical Features Monitoring (CFM)**	**Non-randomised cohort**	**Effect of non-randomised cohort, Incident rate ratio, 95%CI**
Seizure rate per week	392	0 (0,0.26)	0 (0,0.26)	1.0 (0.84,1.4)
Days with seizures per week	393	0 (0,0.23)	0 (0,0.19)	0.88 (0.62,1.2)

3.6 SERIOUS ADVERSE OUTCOMES

Sixty one women experienced one or more serious adverse outcomes between time of consent and 6 weeks postnatal.

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

Other maternal adverse outcomes made up approximately a quarter of serious adverse outcomes in each group. Similarly, congenital malformation contributed almost a quarter to each group although less frequent in the CFM 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 15: Serious adverse outcomes (SAE)

SAE description (Number of women N=61)	Randomised Group		Non-randomised cohort N=25
	Therapeutic Drug Monitoring (TDM) N=19	Clinical Features Monitoring (CFM) N=17	
	No. of women (%)	No. of women (%)	No. of women (%)
Admission to HDU/ITU	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*	1 (5)	1 (6)	1 (4)
Other maternal adverse outcome†	5 (26)	4 (24)	6 (24)

Percentages do not add up to 100 as some women may contribute to more than one SAE category.
No SAE were related to the trial.

* Suspected fetal anaemia, spontaneous pneumothorax, infection

† Post-operative wound infection, suspected cholestasis, bipolar condition, postpartum haemorrhage PV bleed, ankle/fibula injury, IUGR twins, UTI 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 Crohns disease, cervical suture, high blood pressure

CHAPTER 4 QUALITATIVE STUDY

4.1 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 anti-epileptic drugs (AEDs) within in 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 whilst managing their epilepsy. Qualitative data provides 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 life. The growth of qualitative studies within quantitative randomised controlled trial (RCT) framework is important, especially in trials, such as EMPiRE, which are conducted within sensitive settings of maternal and fetal medicine, where participants may be considered 'vulnerable'. [22] 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.

4.1.1 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.[23, 24]. Expert reviews [25, 26] and guidelines [27] 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 [28] in this area was conducted in 2013 and found only one study [29] that directly investigated women's experiences of epilepsy during pregnancy. This 'exploratory qualitative' study, carried out by Thompson et al., investigated the experiences of women living with epilepsy of health care services at key phases of reproduction, [29] including: contraception, pre-conceptual care, pregnancy, birth and breast-feeding, and parenting and child safety. Women reported mixed experiences of healthcare during these stages; some felt 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. argue that the management of a chronic illness and reproductive health involves work of a 'moral dimension'.[29] 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 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 included studies exploring not only women's experiences of pregnancy, but also their experiences of reproductive health whilst managing epilepsy. This expansion of the review resulted in 16 additional publications, which were limited in their generalisability due to small sample sizes and/or poor quality of data. [28] Since the publication of this review, one additional study has been published in this area: Qiang et al.'s 2016 [30] 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.

4.1.2 STUDY AIM

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

4.1.3 OBJECTIVES

To gain insight into the way pregnant women with epilepsy rationalise and make sense of the management of AED 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 influence 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?

4.2 METHODOLOGY

The above research questions were explored empirically through semi-structured interviews using participant narratives.[31] 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.[32]

4.2.1 SAMPLE

Theoretical sampling was employed to purposely include women from different geographical regions, with a diversity of socio-cultural backgrounds, and who had varied histories with epilepsy and had experienced a range of neurological symptoms. Thirty-two women in total 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. [33] Saturation was determined independently by the EMPiRE qualitative lead, Prof. Elaine Denny (ED) and research fellow, Dr. Annalise Weckesser (AW). Women were first approached face-to-face by research nurses and midwives and given informed consent forms for the qualitative study. AW then telephoned women who had agreed to take part in the qualitative study and who had signed informed consent forms.

4.2.2 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 to three interviews, which were audio-recorded with their permission and transcribed verbatim. AW or ED interviewed women twice. AW and ED are both women with experience conducting qualitative research. AW and ED did not establish relationships with participants prior to the commencement of the study. Participants knew AW and ED were non-clinical members of the EMPiRE 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 six weeks after participants had given birth. First interviews lasted approximately one hour and the second interviews lasted approximately a half 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 phone. 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 phone as this was most convenient for women with the time constraints of caring for their new-born. In appreciation for their time and participation, women were given a £20 gift voucher following completion of their first interview.

First interviews took place upon women's entry or refusal of randomised trial, and these interviews focused on the five research questions (*see section 4.1.3*). Additional interviews were originally proposed with women in the qualitative study who had experienced a fall in serum AED or who experienced a seizure during pregnancy to explore whether 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 AW and ED when a patient had a seizure in pregnancy. However, in postnatal interviews AW and ED learned that 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 upon once the outcome of the pregnancy is known. Short field notes were taken immediately after first and second interviews to make note of and describe where interviews took place.

ED and AW developed interview guides to ensure data collection on relevant topics (*see Appendix 10*), but participants were also free to raise issues of importance to them. The interview guide was developed based on themes identified in review of qualitative literature on the experiences of pregnancy and reproductive health of women living with epilepsy,

which was published by ED and AW in 2013. [28] Basic demographic data including current age, parity, and years living with epilepsy were collected from participants at the beginning of the first interview.

4.2.3 ETHICAL CONSIDERATIONS

As epilepsy is considered to be a stigmatising condition [34] 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 statement of ethical practice. [35] Pseudonyms have been used to protect the anonymity of participants.

4.2.4 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'. [36] Within this narrative mode of analysis, a *thematic* approach was undertaken; a method that allowed for the identification of common themes across cases whilst enabling individual women's stories to remain intact.[37] To ensure rigour in the analysis process and to establish trustworthiness in the findings, ED, AW and a member of the EMPiRE trial team read all interview transcriptions. AW took the lead in developing the analysis to increase internal consistency, but all members agreed upon coding frames and analytical themes for internal validity. AW created a coding frame for categorisation of data using NVivo. Analytical themes and concepts were developed and explored using the constant comparison method. [38] An additional strand of narrative analysis was also conducted, allowing for the integrity of each woman's interview to be maintained. [37] 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 (*ibid*). 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.

4.3 FINDINGS

4.3.1 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 15

provides the socio-demographic 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. Women ranged in ages; the youngest participant was 19 years old and the oldest was 42 (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 were 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 interview translation.

Table 16: Sociodemographic background of study sample

Sample (n=560)		
Age (years)	-Range	19-42
	-Mean	31
Marital Status	-Married	18
	-Cohabiting	10
	-Non-Cohabiting/ with partner	2
Parity	-Primigravida	18
	-Gravida 2, Parity 1	10
	-Gravida 3, Parity 2	4
Employment	-Professional	17
	-Retail	2
	-Student	1
	-Unemployed/ FT mother	12
Ethnicity	-White British	21
	-British Asian	4
	-White European	1
	-White American	1
	-Black African	1
	-Chinese	1
	-British-Black Caribbean	1
	-Range	1-29

Years with Epilepsy	-Mean	11.2
Types of Seizures *	-One-off seizure	1
	-Absence seizures	9
	-Myoclonic	9
	-Tonic/clonic (self-defined)	17

* *Some women report more than one type*

Participants had varied histories with epilepsy. One mother was only being diagnosed 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 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 ranged between women and for individual women over time.

4.3.2 INTERVIEW FINDINGS

The following findings are based on antenatal and postnatal interviews. For the purposes of this report 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
- Concerns in relation to epilepsy management in pregnancy
- Strategies for balancing risks & benefits to themselves & their babies in relation to medication
- Perceptions of maternal responsibility in the context of having epilepsy
- Influences on decision-making in the management of epilepsy & pregnancy
- Postnatal reflections on the experience of pregnancy & childbirth & the management of epilepsy

- Reasons for declining trial participation (For participants who have declined participation in randomised trial)

While 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.

4.3.3 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*). While some women had been diagnosed in childhood, others did not receive a diagnosis until more recently and/or after a first pregnancy.

In regards to how the management of their condition impacted upon 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,)

For some, epilepsy impacted upon 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 should she 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 upon them greatly. Some made modifications to their lifestyle (ensuring they get enough sleep, refraining from excessive alcohol consumption, not bathing alone, et cetera) 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 only ever having experienced 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 40s, 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, "Okay 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 upon their day-to-day life, including Tourette's 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 so 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 socio-cultural and religious backgrounds. One participant believed her epilepsy had been caused by a curse and attended evangelical faith healing sessions. Another participant, Amina aged 31, after being diagnosed with the condition reported becoming a more 'devout' practicing 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 they have additional health and fertility concerns and their socio-cultural backgrounds.

4.3.4 CONCERNS IN RELATION TO EPILEPSY MANAGEMENT AND PREGNANCY

As discussed above, 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's. This is illustrated by the case of Philomena, aged 31, 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 that for some may have been 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. While 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 four or five 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 onto 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 onto 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)

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 the affect the baby and me as well.*' Participants worried that a seizure could cause a fall or a reduction in the amount of oxygen that gets to the foetus. 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 due to taking care of her first born 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 one 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 percent 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 license in the event of a seizure.

4.3.5 STRATEGIES FOR BALANCING RISKS & BENEFITS TO THEMSELVES & THEIR BABIES IN RELATION TO MEDICATION

Many of the participants reported thinking about whether 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 with other aspects of their life. Some women felt it was particularly important to keep taking their medication during their pregnancy to minimize 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 you 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, while 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 due to the perception that the foetus was at heightened risk to malformations at this time:
'When I found out I was pregnant with [my first child], I did stop taking [the medication] 'til after my three month scan, and I did do this time as well for the current pregnancy … I went to the [clinic] at about ten weeks pregnant and [the epilepsy nurse] said, 'Have you had any seizures?' I said, 'No'. She said, 'You know you're more susceptible, et cetera, et cetera?' And I said, 'Yes.' And she said, 'Well I'm going to leave you to it.' And then ten 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 license. One participant, Sandra, had a seizure during her first pregnancy, and when 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 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.

4.3.6 PERCEPTIONS OF MATERNAL RESPONSIBILITY IN THE CONTEXT OF HAVING EPILEPSY

While 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] 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)

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 your that you're talking about anymore, 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 anymore, 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)

4.3.7 INFLUENCES ON DECISION-MAKING IN THE MANAGEMENT OF EPILEPSY & 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 that were also informed by knowledge of their own body, history with the condition and seizure warning symptoms. Women's decisions, as discussed above, were also shaped by considerations for the wellbeing 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 that 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.

4.3.8 POSTNATAL REFLECTIONS ON THE EXPERIENCE OF PREGNANCY & CHILDBIRTH & 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 whilst managing epilepsy were largely positive. This is reflected by Jeannette who stated six-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, '*[A] 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 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*.’

While 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 due to 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 new-born infant. While a few wards allowed partners/family members to remain outside of visiting hours, this was not universally practiced across all wards. One woman reported that she felt that she would not have another baby due to her poor postnatal care experience.

In relation to caring for their new-borns, many women reported having to make accommodations due to 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 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 whilst taking AEDs.

Precautionary practices in the day-to-day care of new-borns, 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.

4.3.9 REASONS FOR DECLINING PARTICIPATION IN 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 CFM strategy of the trial, and would have their medication dosage increased only after a seizure and not when their blood levels fell, 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)

'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:

- Work and time commitments (n=1)
- Lived too far from hospital for required monthly antenatal visits (n=1)
- Fear of needles (n=1)
- Stopped taking AEDs prior to pregnancy and did not want to resume (n=1)
- Believed she did not have epilepsy (n=1)

4.4 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 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 babies.

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 show above, 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 [29] study that found 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.'

4.4.1 STRENGTHS & 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.[39]

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 only captured 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, where there has previously been a dearth of robust, in-depth qualitative research. [28] To our knowledge, this constitutes one of only two studies to directly examine women's experiences of pregnancy whilst managing epilepsy. [29]

CHAPTER 5 DISCUSSION

In pregnant women with epilepsy on AED, a strategy of additional therapeutic drug monitoring (TDM) did not significantly reduce the risk of time to first or to multiple seizures compared to management based on clinical features alone. Babies born to mothers with TDM in pregnancy were exposed to significantly high levels of the AEDs lamotrigine and levetiracetam at birth. The average doses of AED prescribed in both groups were similar. There were no differences in pregnancy complications, maternal quality of life measure, birth weight and breast-feeding rates between the two strategies. The risk of seizure was not greater in the groups with a fall in serum AED levels than the stable group, when the CFM and TDM 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.

EMPiRE 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.

5.1 STRENGTHS AND LIMITATIONS

We included women on AEDs that are commonly prescribed in pregnancy, with evidence of fall in levels in pregnancy, and availability of serum level measurements in the NHS.

We excluded women on sodium valproate (VPA), as VPA levels in pregnancy are considered to be unreliable, and is not standard practice in the UK to test serum VPA 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. [39] 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 [40] 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 primary outcome when limited to only tonic clonic seizures. By not pre-specifying the dose of AED to be increased in the TDM group, we provided clinicians the flexibility needed to exercise judgement on how to readjust dose taking into account patient preferences, and factors other than serum AED level that impinges on the decision. EMPiRE study assessed the effect of two strategies on pregnancy outcomes and is the first trial to assess quality of life in mothers with epilepsy on AED.

We randomised fewer women (n=403) than the required target (n=660) to provide definitive evidence on reduction in time to first seizure by at least 25%. An important clinical effect can not be ruled out as indicated by the inclusion of target hazard ratio 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. Due 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 fallen. Although we preferred to use pre-pregnancy levels of AED as the baseline measure against which to compare future levels to detect any fall, in practice, few had pre-pregnancy levels of AED. We accepted AED levels at baseline in pregnancy as the alternative, but it is likely that we may have missed the fall in AED in these cases. However, our approach was pragmatic, reflecting current clinical practice, where 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 seizure risks separately as per AED intake. We pre-specified 25% fall in serum AED level as the threshold for randomising women, determined by consensus involving neurologists. It is

possible, that the effect size would be different for other cut-offs. 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 on the superiority of one strategy over other. This could be one of the reasons for slow recruitment.

Women's views for declining participation in 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 CFM strategy of the trial, and would have their medication dosage increased only after a seizure and not when their blood levels fell. They believed not increasing their medication when their blood levels fell 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.

Falls in serum AED level in pregnancy and seizure deterioration

Serum AED concentrations often fall during pregnancy. Physiological changes in pregnancy alter AED pharmacokinetics and AED concentrations. There is decreased gastric tone and motility, increased plasma volume, increased renal clearance and albumin levels and protein binding. [8, 13, 41, 42] The falls in serum AED levels are considered to aggravate seizures. [43] 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. [43] In the UK however, the SIGN (Scottish Intercollegiate Guidelines Network) guideline does not recommend regular AED monitoring in pregnancy due to a paucity of evidence. [11] Our systematic review on the effect of AED monitoring strategies in pregnant women with epilepsy on AED showed lower rates of seizures with TDM than CFM strategies. [44] The studies were not randomised, nor 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, and to multiple tonic clonic showed a trend towards favouring TDM, the findings were not significant.

AED exposure in pregnancy to mother and fetus

Measurement of total AED exposure enabled us to delineate the likelihood of excess exposure under TDM, where dose escalation is expected in response to known fall in serum AED levels. However, no differences were observed between the groups. It is likely that when serum AED levels fell, the intervention in TDM group comprised of either close monitoring or dose escalation, whereas without information on 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 new-born in TDM group were higher for the commonly prescribed AEDs, lamotrigine and levetiracetam. The developmental quotient of infants of mothers exposed to lamotrigine in pregnancy compared to women without epilepsy and women not on AED appeared to be similar in a small study. [45] There is limited evidence to assess the effect of levetiracetam or AED polytherapy on long-term neurodevelopment. [46]

Quality of life in women with AED

Effect of seizures extends into daily living resulting in loss of driving license and are known to have a negative impact on employment and relationships and reduced Quality of Life (QoL). [47] We found no differences in the scores for quality of life between the two groups. The additional information on AED levels in pregnancy and the subsequent management based on it, it did not appear to adversely affect women's quality of life.

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. [48] This is particularly relevant for pregnant women with epilepsy. Our survey of epilepsy specialists (n=29) in the UK showed that a third of participants managed women with epilepsy on AED with regular therapeutic monitoring of drug levels, a third adjusted doses based on clinical features only and the rest used TDM occasionally. [49] Given the wide confidence intervals, reflecting the imprecision, the absence of differences between the two strategies, and similar rates of seizures in women with stable and fall in serum AED levels, we are not able to advocate routine TDM monitoring in pregnancy.

Although we randomised only half the number of women required to provide the definitive answer, given the wide imprecision in the confidence intervals, we do not expect one strategy to be shown to be significantly effective than 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% reduction in seizures, as postulated in our sample size calculation. Only 36 women should have suffered seizures compared to 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 standard deviation holds, we estimate that 1038 and 1302 women would have been required to demonstrate a significant effect in time to first and any seizure respectively, for TDM vs. CFM.

The risk of seizure deterioration was not significantly different between the non-randomised group with stable AED levels, compared to those with a fall of 25% or more, reinforcing the lack of benefit with 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 TDM. 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. Women with epilepsy on AEDs require management in a multidisciplinary setting, with a team involved in both care of their pregnancy and their seizures.

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

- *Preconception information*: Preconception 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 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 that women's decisions to stop, reduce, maintain and/or increase their

AEDs over the course of their pregnancies, are based on a rationale of maternal responsibility towards their babies.

- *Postnatal care*: A review of postnatal ward policies and practices on accommodating women with epilepsy would be beneficial on access to family and partners are needed.
- *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, et cetera) 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 over 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 fall in AED need further evaluation. A robust risk assessment method, using an individualised prediction model by taking into account mother's clinical characteristics including type and duration of seizure, type of AED and change in 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 healthcare 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 only included women who had chosen 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. Furthermore, there is a need for more 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 to 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 arm.

The qualitative study sought to address the dearth of research on women's experiences of pregnancy whilst managing their epilepsy and to date is one of only two studies [29] in this area. 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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CONTRIBUTION OF AUTHORS

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 Coordinator) 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, provided clinical advice.

Lynette Greenhill (Lead epilepsy specialist nurse) assisted with the design of the trial and provided advise and support.

Rachel Rikunenko (Trial Coordinator) 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 coordinator) supported the trial and its data collection and contributed to the final report.

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

Kelly Hard (R&D manager) assisted with the design of the trial and provided advise and support towards the report.

Jamie Coleman (Clinical pharmacologist) delivered support in developing the trial, provided clinical direction.

Ngawai Moss (Patient and public representative) provided support and advice throughout the trial and provided input towards the final report.

Tracy Roberts (Lead health economist) assisted with the design of the trial and provided advise and support towards the report.

Lee Middleton (Statistician) supported the development of the trial, provided statistical direction and contributed to the report.

Julie Dodds (Senior research manager) supervised the running of the trial, provided direction and support and contributed to the final report.

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.

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

DATA SHARING

Study data can be obtained from the corresponding author.

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APPENDIX 1 DEFINITION OF THE PRIMARY OUTCOME

Table 17: Definition of the primary outcome

Outcome	Definition
Time from randomisation to first tonic-clonic	Time between a 25% drop in serum AED levels and the first tonic-clonic seizure. A tonic-clonic seizure (or Grand Mal seizure) is a common generalised seizure, meaning 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% drop in serum AED levels and the first seizure that is not a tonic-clonic. 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 that typically involve muscle jerks and can occur in clusters. Focal seizures include Complex partial seizures (CPS) where consciousness is affected and involuntary movements (Automatisms) such as lip smacking. During a Simple partial seizure (SPS), the person is aware and alert and symptoms vary dependent on the area of the brain affected.

APPENDIX 2 LIST OF CORE OUTCOMES FOR STUDIES ON PREGNANT WOMEN WITH EPILEPSY (DELPHI).

Table 18: Core of outcomes for studies on pregnant women with Epilepsy (DELPHI)

Neurological outcomes	Foetal and neonatal outcomes	Obstetric outcomes
AED toxicity*	Admission to neonatal intensive care unit.	Admission to high dependency or intensive care unit
Compliance with AED *	Autism spectrum disorder	Breastfeeding rate*
Drowning	Anthropometric measurements including birth weight	Hypertensive disorder (Pre-eclampsia, Eclampsia)
Maternal death	Fetal anticonvulsant syndrome*	Pregnancy outcome (Live birth rate, Ectopic pregnancy, Miscarriage, Termination of pregnancy)
Postnatal depression	Congenital abnormalities (Major and Minor)	Mode of delivery
Seizure control (Postpartum and in pregnancy)	Neonatal haemorrhagic disease*	Pre-term birth
Quality of life	Neurodevelopment*	
Status epilepticus	Neonatal withdrawal symptoms*	
SUDEP[1]	Neonatal clinical complications [2]	
	Stillbirth	

* Outcomes applicable only in studies on pregnant women on anti-epileptic agents.
[1] Sudden unexpected death in epilepsy
[2]Acute respiratory distress syndrome, anaemia, hypoglycemia, hyperglycemia, hypocalcemia, hypotonia, feeding problems, sedation syndrome, icterus/convulsions, cephalheamatoma and apgar scores.
http://www.bjog.org/view/0/crown-initiative.html Accessed on 6 June 2016.

APPENDIX 3 LIST OF COLLABORATORS

EMPIRE collaborative Network: Shanika Samarasekera - Queen Elizabeth Hospital, Birmingham; Rajat Gupta - Birmingham Childrens Hospital, Birmingham; Naghme Adab - University Hospital of Coventry and Warwickshire; Ismail Khaled - Keel University Medical School and University of North Staffordshire; Lee Middleton - Birmingham University, Birmingham; Manjo Doug - Birmingham Womens NHS Foundation Trust, Birmingham; Tracy Baker - Birmingham; Dr Salwa El-Taher - Arrowe Park Hospital, Wirral; Dr Catharina Schram - Royal Blackburn 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 Catharina Schram - Burnley General Hospital, Lancashire; 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; 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, 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 Sophie Stone - St Richard's Hospital, Chichester; Dr Philippa Marsden - Royal Victoria Infirmary, Newcastle; 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; Mr Phil Tittensor - Stafford General Hospital, Stafford; Dr Adam Gornall - Royal Shrewsbury

Hospital, Shrewsbury; Dr Aylur Rajasri - Royal Cornwall Hospital (Treliske), Truro; 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 4 AMENDMENTS TO PROTOCOL

Table 19: 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 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 this data will be parked until further funding is available.
3. Bayley scales of infant development (BSID) was being used to assess mental and motor development of the infant at the 6 week postnatal visit.	It was agreed by the trial steering committee 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 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 level on antiepileptic drug transferred from 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 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 where 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 practise, 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 32-36 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 inclusion criteria original stated that women who have a confirmed viable pregnancy of less than 16 weeks gestation can be recruited.	This was amended to include women who have a confirmed viable pregnancy of less than 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.
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 Group A and 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 post-natal visit could be conducted at any point between 6-8 weeks post-delivery.

The trial protocol is available at http://www.nets.nihr.ac.uk/projects/hta/095538. Accessed on 6 June 2016.

APPENDIX 5 RECRUITMENT AT EACH SITE

Table 20: Breakdown of recruitment by site

Site	TDM N=130	CFM N=133	Non randomised N=294	Total N=557
Arrow 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
Queen Alexandra Hospital	2	0	3	5
Queen's Hospital	7	7	13	27
St. Richards 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 Georges 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

APPENDIX 6 MATERNAL OUTCOMES

Table 21: Maternal adverse effects of AED exposure - lamotrigine alone

Outcome		N mother	Mean LTG exposure (SD)		Measure*	Effect of increasing exposure, 95%CI
			No outcome	Outcome		
LAEP score		178	N/A	N/A	IRR	1.0 (1.0,1.0)
Gestational age at delivery		257	N/A	N/A	MD	0.00 (-0.00,0.02)
CS or instrumental delivery		255	273 (153)	287 (156)	OR	1.0 (1.0,1.0)
Preterm labour		249	281 (155)	253 (149)	OR	0.9991.0 (1.0,1.0)
Induction of labour		254	273 (151)	301 (165)	OR	1.0 (1.0,1.0)
Pre-eclampsia		248	279 (154)	293 (165)	OR	1.0 (1.0,1.0)
Gestational diabetes mellitus		248	276 (150)	374 (234)	OR	1.0 (1.0,1.0)
Antepartum haemorrhage		187	277 (154)	351 (172)	OR	1.0 (1.0,1.0)
Postpartum haemorrhage		254	272 (152)	312 (159)	OR	1.0 (1.0,1.0)
Admission to HDU or ICU		249	277 (154)	310 (160)	OR	1.0 (1.0,1.0)
Breast feeding	Breast	253	264 (132)		OR	1.0 (1.0,1.0)
	Mixed		300 (177)			
	Bottle		309 (186)			

* IRR – Incidence rate ratio, MD – Mean difference, OR – Odds ratio

clustering of multiple foetuses by mother ignored due to convergence issues

Table 22: Mean difference AED exposure by occurrence of maternal adverse events - Lamotrigine alone

Adverse events	N mother	Mean difference in LTG exposure, 95%CI
CS or instrumental delivery	255	24.1 (-12.5,60.8)
Preterm labour	256	-11.2 (-85.3,62.9)
Induction of labour	254	22.2 (-20.0,64.4)
Pre-eclampsia	255	14.8 (-89.4,119.0)
Gestational diabetes mellitus	255	50.0 (-46.0,146.0)
Antepartum haemorrhage	254	100.9 (-3.8,205.6)

Postpartum haemorrhage		254	49.2 (-0.8,99.2)
Admission to HDU or ICU		256	31.6 (-49.5,112.7)
	Breast		Reference group
Breast feeding	Mixed	253	33.3 (-25.7,92.3)
	Bottle		38.8 (-4.6,82.1)

Table 23: Maternal adverse effects of AED exposure - levetiracetam alone

Outcome		N mother	Mean LEV exposure (SD)		Measure*	Effect of increasing exposure, 95%CI
			No outcome	Outcome		
Maternal						
LAEP score		88	N/A	N/A	IRR	1.0 (1.0,1.0)
Gestational age at delivery		126	N/A	N/A	MD	-0.0 (-0.0,0.0)
CS or instrumental delivery		124	1740 (987)	1548 (641)	OR	1.0 (1.0,1.0)
Preterm labour		96	1634 (864)	1888 (639)	OR	1.0 (1.0,1.0)
Induction of labour		125	1620 (868)	1694 (834)	OR	1.0 (1.000,1.0)
Pre-eclampsia		51	1645 (859)	1825 (459)	OR	1.0 (1.0,1.0)
Gestational diabetes mellitus		124	1627 (807)	1471 (611)	OR	1.0 (0.998,1.0)
Antepartum haemorrhage		70	1639 (859)	2033 (454)	OR	1.0 (1.0,1.0)
Postpartum haemorrhage		127	1684 (890)	1396 (470)	OR	0.9991.0 (1.0,1.0)
Admission to HDU or ICU		125	1662 (858)	1314 (715)	OR	0.9991.0 (1.0,1.0)
	Breast		1599 (897)			
Breast feeding	Mixed	125	1928 (1022)		OR	1.000 (1.0,1.0)
	Bottle		1611 (592)			

* IRR – Incidence rate ratio, MD – Mean difference, OR – Odds ratio

clustering of multiple foetuses by mother ignored due to convergence issues

Table 24: Mean difference AED exposure by occurrence of maternal adverse events - levetiracetam alone

Adverse events	N mother	Mean difference in LEV exposure, 95%CI
Maternal		
CS or instrumental delivery	126	-226.4 (-536.3,83.5)

Preterm labour		127	23.6 (-644.4,691.5)
Induction of labour		127	7.7 (-307.4,322.8)
Pre-eclampsia		127	358.0 (-823.6,1539.5)
Gestational diabetes mellitus		126	-109.5 (-815.6,596.6)
Antepartum haemorrhage		127	507.2 (-459.5,1473.9)
Postpartum haemorrhage		127	-365.5 (-817.5,86.6)
Admission to HDU or ICU		127	-431.7 (-1184.8,321.5)
	126 (128)		Reference group
Breast feeding	97 (98)	125	246.5 (-153.4,646.5)
	50 (51)		-28.5 (-382.0,325.0)

Table 25: Maternal adverse effects of AED exposure - carbamazepine alone

Outcome		**N mother**	**Mean CBZ exposure (SD)**		**Measure***	**Effect of increasing exposure, 95%CI**
			No outcome	Outcome		
Maternal						
LAEP score		60	N/A[2]	N/A	IRR	1.0 (1.0,1.0)
Gestational age at delivery		86	N/A	N/A	MD	-0.01 (-0.02,0.0)
CS or instrumental delivery		86	632 (317)	711 (290)	OR	1.0 (1.0,1.0)
Preterm labour		82	647 (295)	842 (315)	OR	1.0 (1.0,1.0)
Induction of labour		82	631 (274)	747 (340)	OR	1.0 (0.1,1.0)
Pre-eclampsia		81	676 (305)	604 (303)	OR	1.0 (0.1,1.0)
Gestational diabetes mellitus		63	665 (305)	831 (249)	OR	1.0 (1.0,1.0)
Antepartum haemorrhage		63	671 (305)	800 (283)	OR	1.0 (0.98,1.06)
Postpartum haemorrhage		82	664 (297)	764 (363)	OR	1.0 (1.0,1.0)
Admission to HDU or ICU		63	676 (308)	623 (167)	OR	1.0 (0.99,1.01)
Breast feeding	Breast	85	689 (336)		OR	1.0 (1.0,1.0)
	Mixed		634 (275)			
	Bottle		665 (174)			

* IRR – Incidence rate ratio, MD – Mean difference, OR – Odds ratio

clustering of multiple foetuses by mother ignored due to convergence issues

[1] Not applicable as outcome and exposure variable are continuous

Table 26: Mean difference AED exposure by occurrence of maternal adverse events - carbamazepine alone

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

Table 27: Maternal adverse effects of AED exposure - lamotrigine & levetiracetam

Outcome	N mother (N baby)	Measure*	Mean LTG exposure (SD)		Effect of increasing exposure, 95%CI	Mean LEV exposure (SD)		Effect of increasing exposure, 95%CI
			No outcome	Outcome		No outcome	Outcome	
Maternal								
LAEP score	22	IRR	N/A	N/A	1.0 (1.000,1.001)	N/A	N/A	1.0 (1.0,1.0)
Gestational age at delivery	36	MD	N/A	N/A	-0.01 (-0.050,0.030)	N/A	N/A	-0.0 (-0.01,0.00)
CS or instru-mental delivery	35	OR	376 (169)	451 (177)	1.0 (1.000,1.025)	1867 (913)	2060 (1028)	1.0 (1.0,1.0)
Preterm labour	35	OR	421 (175)	424 (190)	1.0 (0.995,1.008)	1880 (873)	2508 (1364)	1.0 (1.0,1.0)

Induction of labour		35	OR	420 (205)	423 (129)	0.9991.0 (0.99,1.0	2053 (1137)	1889 (720)	1.0 (1.0,1.0)
Pre-eclampsia		23	OR	401 (169)	518 (34)	Prefect prediction	2038 (961)	1743 (1316)	Prefect prediction
Gestational diabetes mellitus		-	OR	410 (167)	450	Prefect prediction	1941 (891)	4462	Prefect prediction
Antepartum haemorrhage		-	OR	422 (178)	400	Prefect prediction	2013 (976)	1000	Prefect prediction
Postpartum haemorrhage		24	OR	387 (161)	566 (169)	1.0 (0.99,1.0)	1967 (963)	2060 (1106)	1.0 (1.0,1.0)
Admission to HDU or ICU		-	OR	423 (180)	400 (0)	Prefect prediction	2028 (986)	1250 (354)	Prefect prediction
Breast feeding	Breast	36	OR	446 (186)			2180 (969)		0.9991.0 (1.0,1.0)
	Mixed			523			2000		
	Bottle			404 (174)		0.99 (0.99,1.0)	1882 (1008)		

* IRR – Incidence rate ratio, MD – Mean difference, OR – Odds ratio
# clustering of multiple foetuses by mother ignored due to convergence issues

Table 28: Mean difference AED exposure by occurrence of maternal adverse events lamotrigine & levetiracetam

Adverse events	N mother	Mean difference in LTG exposure, 95%CI	Mean difference in LEV exposure, 95%CI
Maternal			
CS or instrumental delivery	36	87.3 (-46.8,221.5)	30.5 (-771.0,832.0)
Preterm labour	36	15.3 (-146.4,177.0)	557.0 (-355.7,1469.7)
Induction of labour	36	-23.1 (-173.1,126.9)	87.0 (-783.1,957.2)
Pre-eclampsia	35	124.0 (-84.2,332.3)	-5.1 (-1337.0,1326.8)
Gestational diabetes mellitus	35	-89.4 (-460.1,281.4)	2205.7 (56.8,4354.7)
Antepartum haemorrhage	36	79.1 (-340.6,498.8)	-919.0 (-3331.4,1493.4)
Postpartum haemorrhage	36	142.8 (-11.6,297.2)	-253.6 (-1198.7,691.5)

Admission to HDU or ICU		36	48.8 (-247.2,344.9)	-593.1 (-2296.9,1110.8)
Breast feeding	Breast	36	Reference group	Reference group
	Mixed		-29.7 (-428.8,369.3)	-332.227 (-2680.7,2016.2)
	Bottle		-74.0 (-209.9,61.9)	-250.6 (-1050.4,549.3)

APPENDIX 7 FETAL OUTCOMES

Table 29: Fetal adverse effects of AED exposure - lamotrigine alone

Outcome	N mother (N baby)	Mean LTG exposure (SD)		Measure*	Effect of increasing exposure, 95%CI
		No outcome	Outcome		
Fetal					
Cord blood levels LTG (mg/L)	186(188)	N/A	N/A	MD	0.01 (0.01,0.01)
Major congenital malformations	247 (254)	276 (156)	302 (116)	OR#	1.0 (1.0,1.01)
Baby's admission to neonatal unit	254 (247)	279 (153)	273 (162)	OR	1.0 (1.0,1.0)
Apgar score at 1'	247 (252)	N/A	N/A	MD	-1e-4 (-0.00,0.00)
Apgar score at 5'	249 (254)	N/A	N/A	MD	3e-4 (-0.00,0.00)
Birth weight in kg	254 (261)	N/A	N/A	MD	4e-4 (-2e-4,0.00)
Birth weight centile <10th centile	254 (261)	279 (152)	268 (170)	OR	0.9981.0 (1.0,1.0)
Head circumference in cm	202 (206)	N/A	N/A	MD	-1e-4 (-0.00,0.00)
Cord Ph A	103 (104)	N/A	N/A	MD	-2e-4 (-3e-4,7e-6)
Cord Ph V	109 (110)	N/A	N/A	MD#	-2e-4 (-3e-4,-3e-5)

* IRR – Incidence rate ratio, MD – Mean difference, OR – Odds ratio

clustering of multiple foetuses by mother ignored due to convergence issues

Table 30: Mean difference AED exposure by occurrence of fetal adverse events - lamotrigine alone

Adverse events	N mother (N baby)	Mean difference in LTG exposure, 95%CI
Fetal		
Major congenital malformations	247 (254)	39.0 (-31.6,109.6)
Baby's admission to neonatal unit	254 (247)	4.2 (-53.5,61.8)
Apgar score at 1' <7	247 (252)	9.0 (-73.5,91.5)
Apgar score at 5' <7	249 (254)	90.9 (-40.5,222.3)
Birth weight centile <10th centile	254 (261)	-33.4 (-94.5,27.7)

Cord Ph A <7	103 (104)	-144.9 (-356.6,66.8)
Cord Ph V <7	109 (110)	-77.2 (-388.1,233.7)

Table 31: Fetal adverse effects of AED exposure - levetiracetam alone

Outcome	N mother (N baby)	Mean LEV exposure (SD)		Measure*	Effect of increasing exposure, 95%CI
		No outcome	Outcome		
Fetal					
Cord blood levels LEV (mg/L)	94 (95)	N/A	N/A	MD#	**0.01 (0.01,0.01)**
Major congenital malformations	126 (128)	1646 (858)	1859 (593)	OR	1.0 (1.0,1.01)
Baby's admission to neonatal unit	124 (126)	1626 (789)	2063 (1415)	OR	1.0 (1.0,1.0)
Apgar score at 1'	123 (125)	N/A	N/A	MD#	-8e-6 (-3e-4, 3e-4)
Apgar score at 5'	123(125)	N/A	N/A	MD#	-4e-5 (-2e-4,1e-4)
Birth weight in kg	126 (128)	N/A	N/A	MD	6e-5 (-3e-5,2e-4)
Birth weight centile <10th centile	126 (128)	1609 (804)	1928 (1041)	OR	1.0 (1.0,1.0)
Head circumference in cm	97 (98)	N/A	N/A	MD#	3e-4 (-7e-5,0.001)
Cord Ph A	50 (51)	N/A	N/A	MD#	-0.005 (-0.01,0.00)
Cord Ph V	59 (61)	N/A	N/A	MD	-0.003 (-0.01,0.00)

* IRR – Incidence rate ratio, MD – Mean difference, OR – Odds ratio

clustering of multiple foetuses by mother ignored due to convergence issues

Table 32: Mean difference AED exposure by occurrence of fetal adverse events - levetiracetam alone

Adverse events	N mother (N baby)	Mean difference in LEV exposure, 95%CI
Fetal		
Major congenital malformations	126 (128)	149.3 (-572.1,870.6)
Baby's admission to neonatal unit	124 (126)	362.2 (-206.5,930.9)
Apgar score at 1' <7	123 (125)	-47.5 (-638.2,543.2)

Apgar score at 5' <7	123(125)	Perfect prediction
Birth weight centile <10th centile	126 (128)	225.4 (-216.0,666.8)
Cord Ph A <7	50 (51)	Perfect prediction
Cord Ph V <7	59 (61)	Perfect prediction

Table 33: Fetal adverse effects of AED exposure - carbamazepine alone (in bold statistically significant results at 5% level)

Outcome	N mother (N baby)	Mean CBZ exposure (SD)		Measure*	Effect of increasing exposure, 95%CI
		No outcome	Outcome		
Fetal					
Cord blood levels CBZ (mg/L)	62 (64)	N/A	N/A	MD#	**0.00 (0.00,0.00)**
Major congenital malformations	85 (88)	670 (285)	688 (398)	OR	1.0 (1.0,1.0)
Baby's admission to neonatal unit	85 (88)	677 (290)	644 (358)	OR	0.9991.0 (0.99,1.0)
Apgar score at 1'	84 (87)	N/A	N/A	MD	-0.00 (-0.00,0.00)
Apgar score at 5'	84 (87)	N/A	N/A	MD#	-9e-5 (-0.00,0.00)
Birth weight in kg	85 (88)	N/A	N/A	MD	-0.00 (-0.00,-0.00)
Birth weight centile <10th centile	85 (88)	640 (299)	777 (281)	OR	1.0 (1.0,1.0)
Head circumference in cm	63 (66)	N/A	N/A	MD	-0.00 (-0.00,0.00)
Cord Ph A	35 (36)	N/A	N/A	MD	1e-5 (-1e-4.1e-4)
Cord Ph V	40 (40)	N/A	N/A	MD#	1e-5 (-1e-4.1e-4)

* IRR – Incidence rate ratio, MD – Mean difference, OR – Odds ratio

clustering of multiple foetuses by mother ignored due to convergence issues

Table 34: Fetal adverse effects of AED exposure - carbamazepine alone (in bold statistically significant results at 5% level)

Adverse events	N mother (N baby)	Mean difference in CBZ exposure, 95%CI

Fetal		
Major congenital malformations	85 (88)	-14.1 (-198.9,170.8)
Baby's admission to neonatal unit	85 (88)	-58.8 (-231.4,113.7)
Apgar score at 1' <7	84 (87)	-110.7 (-308.7,87.4)
Apgar score at 5' <7	84 (87)	7.7 (-284.7,300.2)
Birth weight centile <10th centile	85 (88)	132.1 (-5.7,269.9)
Cord Ph A <7	35 (36)	Prefect prediction
Cord Ph V <7	40 (40)	32.8 (-624.2,689.9)

Table 35: Fetal adverse effects of AED exposure - lamotrigine & levetiracetam

Outcome	**N mother (N baby)**	**Measure***	**Mean LTG exposure (SD)**		**Effect of increasing exposure, 95%CI**	**Mean LEV exposure (SD)**		**Effect of increasing exposure, 95%CI**
			No outcome	Outcome		No outcome	Outcome	
Fetal								
Cord blood levels LTG (mg/L)	27	MD	N/A	N/A	**0.009 (0.004,0.013)**	N/A	N/A	-2e-4 (-0.001,0.001)
Cord blood levels LEV (mg/L)					0.008 (-0.026,0.041)			**0.008 (0.002,0.013)**
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 (0.989,1.021)	1841 (767)	2297 (1244)	1.002 (0.998,1.006)
Apgar score at 1'	35 (37)	MD#	N/A	N/A	3e-4 (-0.004,0.005)	N/A	N/A	0.000 (-0.000,0.001)
Apgar score at 5'	35 (37)	MD#	N/A	N/A	0.001 (-0.002,0.003)	N/A	N/A	0.000 (-0.000,0.001)
Birth weight in kg	35 (37)	MD	N/A	N/A	-0.001 (-0.002,0.000)	N/A	N/A	-0.000 (-0.000,0.000)
Birth weight <10th centile	15 (17)	OR	420 (185)	473 (115)	Perfect prediction	1898 (947)	2218 (685)	Perfect prediction
Head circum-ference in cm	27 (28)	MD	N/A	N/A	-0.001 (-0.005,0.002)	N/A	N/A	0.001 (-2e-4,0.001)

Cord Ph A	13 (14)	MD#	N/A	N/A	2e-4 (-3e-4,0.001)	N/A	N/A	6e-5 (-1e-4,2e-4)
Cord Ph V	14 (16)	MD	N/A	N/A	2e-4 (5e-5,3e-4)	N/A	N/A	-3e-5 (-9e-5,2e-5)

* IRR – Incidence rate ratio, MD – Mean difference, OR – Odds ratio

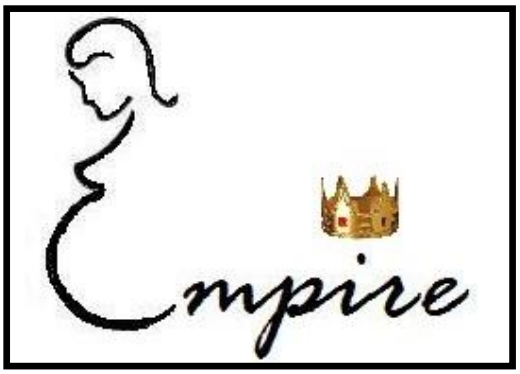
clustering of multiple foetuses by mother ignored due to convergence issues

Table 36: Mean difference AED exposure by occurrence of fetal adverse events lamotrigine & levetiracetam

Adverse events	**N mother (N baby)**	**Mean difference in LTG exposure, 95%CI**	**Mean difference in LEV exposure, 95%CI**
Fetal			
Major congenital malformations	22 (24)	-11.5 (-288.6,265.7)	-317.8 (-1920.0,1284.6)
Baby's admission to neonatal unit	36 (38)	46.2 (-87.5,179.9)	522.5 (-233.5,1278.4)
Apgar score at 1' <7	35 (37)	-42.1 (-239.8,155.5)	964.7 (-53.5,1982.9)
Apgar score at 5' <7	35 (37)	-128.2 (-551.8,295.4)	951.9 (-1351.1,3254.9)
Birth weight centile <10th centile	15 (17)	161.3 (-15.4,338.0)	289.6 (-729.1,1308.2)
Cord Ph A <7	13 (14)	Perfect prediction	Perfect prediction
Cord Ph V <7	14 (16)	Perfect prediction	Perfect prediction

APPENDIX 8 CRF

8.1 BASELINE BOOKLET



BASELINE BOOKLET
Patient UTIN: __ __/__ __ __

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.

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
		__ __/__ __ __	DD / 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		Date AED level taken	Use as the EMPIRE serum target level	
			Value	Unit			
carbamazepine (generic) Yes ☐ No ☐		PPSL ☐		µmol/l ☐ mg/l ☐	DD / MMM / YYYY	Yes ☐ No ☐	
Tegretol (brand) Yes ☐ No ☐		EPSL ☐		µmol/l ☐ mg/l ☐	DD / MMM / YYYY	Yes ☐ No ☐	
Tegretol Retard (brand) Yes ☐ No ☐		Neither ☐					
lamotrigine (generic) Yes ☐ No ☐		PPSL ☐		µmol/l ☐ mg/l ☐	DD / MMM / YYYY	Yes ☐ No ☐	
		EPSL ☐		µmol/l ☐ mg/l ☐	DD / MMM / YYYY	Yes ☐ No ☐	
Lamictal (brand) Yes ☐ No ☐		Neither ☐					
levetiracetam (generic) Yes ☐ No ☐		PPSL ☐		µmol/l ☐ mg/l ☐	DD / MMM / YYYY	Yes ☐ No ☐	
		EPSL ☐		µmol/l ☐ mg/l ☐	DD / MMM / YYYY	Yes ☐ No ☐	
Keppra (brand) Yes ☐ No ☐		Neither ☐					
phenytoin (generic) Yes ☐ No ☐		PPSL ☐		µmol/l ☐ mg/l ☐	DD / MMM / YYYY	Yes ☐ No ☐	
		EPSL ☐		µmol/l ☐ mg/l ☐	DD / 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** ☐

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

BASELINE BOOKLET	Baseline Form Surgical & Obstetric History	Participant UTIN	Visit date
		__ __/__ __ __	DD /MMM /YYYY

SURGICAL HISTORY

Has the participant had any intracranial surgery prior to the study visit?	Yes ☐ No ☐
If yes, please specify	
Date	DD /MMM /YYYY

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** DD /MMM /YYYY

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** ☐

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) Major 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	☐

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
		__ __/__ __ __	DD /MMM /YYYY

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** ☐	

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

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**
		__ __/__ __ __	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
		__ __/__ __ __	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
		__ __/__ __ __	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
		__ __/__ __ __	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** ☐

8.2 NDDI-E

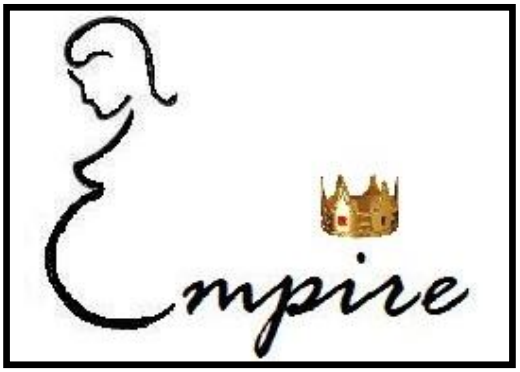
PATIENT'S QUESTIONAIRE	Baseline visit NDDI-E SCREENING TOOL	Participant UTIN	Visit date
		__ __/__ __ __	DD /MMM /YYYY

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

8.3 PATIENT QUESTIONNAIRE



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

PATIENT'S QUESTIONNAIRE	EQ – 5D	Participant UTIN	Visit date
		__ __/__ __ __	DD / MMM / YYYY

EQ – 5D HEALTH QUESTIONNAIRE

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 ❑

PATIENT'S QUESTIONNAIRE	LAEP	Participant UTIN	Visit date
		__ __/__ __ __	DD /MMM /YYYY

LIVERPOOL ADVERSE EVENTS PROFILE (LAEP)

During the last four weeks have you had any of the problems listed below? For each item, if it has always or often been a problem circle 4. If it has sometimes been a problem circle 3 and so on. Please be sure to answer every item.				
	Always or often a problem	Sometimes a problem	Rarely a problem	Never a problem
a) unsteadiness	4	3	2	1
b) tiredness	4	3	2	1
c) restlessness	4	3	2	1
d) feelings of anger or aggression to others	4	3	2	1
e) nervousness or agitation	4	3	2	1
f) headache	4	3	2	1
g) hair loss	4	3	2	1
h) problems with skin (e.g. acne, rash)	4	3	2	1
i) double or blurred vision	4	3	2	1
j) upset stomach	4	3	2	1
k) difficulty in concentrating	4	3	2	1
l) trouble with mouth or gums	4	3	2	1
m) shaky hands	4	3	2	1
n) weight gain	4	3	2	1
o) dizziness	4	3	2	1
p) sleepiness	4	3	2	1
q) depression	4	3	2	1
r) memory problems	4	3	2	1
s) disturbed sleep	4	3	2	1
t) any other problem (please list in the space below and ring the appropriate number to indicate your response				
aa)	4	3	2	1
bb)	4	3	2	1
cc)	4	3	2	1

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

QUESTIONAIRE 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	Cost questionnaire	Participant UTIN	Visit date

QUESTIONNAIRE	Part 2	__ __/__ __ __	DD /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_____

PATIENT'S QUESTIONNAIRE	Cost questionnaire Part 3	Participant UTIN	Visit date
		__ __/__ __ __	DD /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 cost of the (one-way) fare? Put zero 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.

_____

_____

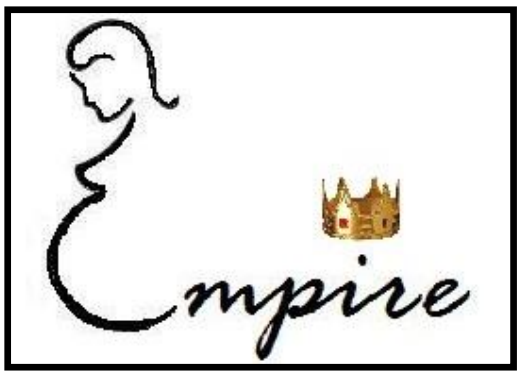
_____

_____

Thank you for taking the time to complete this questionnaire.

5.4 QOLIE – QUALITY OF LIFE IN EPILEPSY

	QOLIE 31	Par



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

Patient UTIN: __ __/__ __ __

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)

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**

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
		__ __/__ __ __	DD /MMM /YYYY

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**

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)*

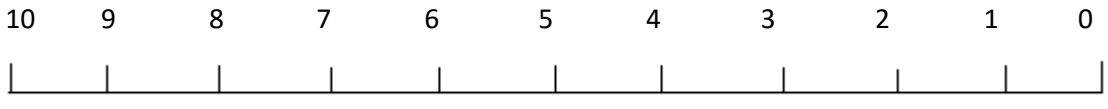
	Very worried	Somewhat worried	Not very worried	Not at all worried
23. How worried are you about embarrassment or other social problems due to a fit during the next 4 weeks?	**1**	**2**	**3**	**4**
24. How worried are you that the drugs you are taking may be bad for you if you have to take them for a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

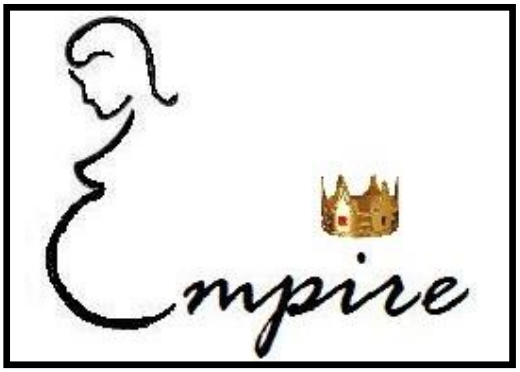
31. How good or bad do you think your health is? On the thermometer scale below, the best imaginable state of health is 10 and the worst imaginable state is 0. Please indicate how you feel about your health by circling one number on the scale. **Please consider your epilepsy as part of your health when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

(Please circle only one number on the scale below)



Best Imaginable Health State Worst Imaginable Health State

8.5 ANTENATAL FOLLOW UP BOOKLET



ANTENATAL FOLLOW-UP BOOKLET
Patient UTIN: __ __/__ __ __

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:***

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
		__ __/__ __ __	DD /MMM /YYYY

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*

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** ☐

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 ☐		**<u>If abnormal,</u> please specify abnormality:**	

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

Was fetal growth measured?	**Yes** ☐ **No** ☐	*If **yes**, please complete the following*	
Date of scan	DD /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		☐

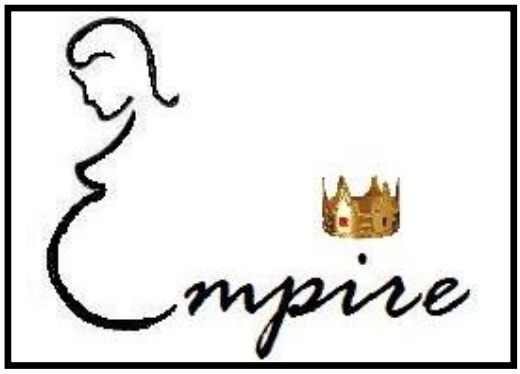
ANTENATAL FOLLOW-UP BOOKLET	Purple alert record	Participant UTIN	Date
		__ __/__ __ __	DD /MMM /YYYY

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:*	

8.6 DELIVERY BOOKLET

	Visit checklist	P



DELIVERY BOOKLET

Patient UTIN: __ __/__ __ __

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

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**	☐

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 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*			

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

BABY DETAILS

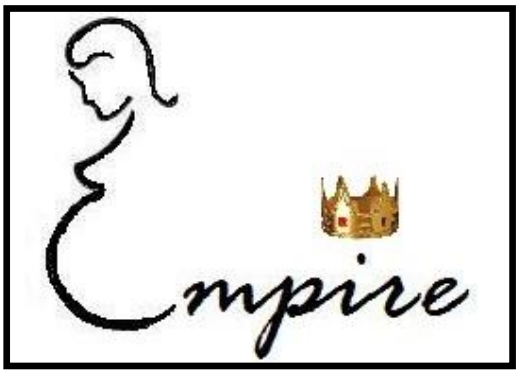
Please use the following sheets to document information about all of the participant's births/children. One sheet should be used per child. Please specify child number between booklet name and participant UTIN.

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*			

8.7 POSTNATAL FOLLOW UP BOOKLET



POSTNATAL FOLLOW-UP BOOKLET
Patient UTIN: __ __/__ __ __

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
		__ __/__ __ __	DD /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_____

POSTNATAL FOLLOW-UP BOOKLET	Post Natal Form	Participant UTIN	Visit date
		__ __/__ __ __	DD /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	**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
		__ __/__ __ __	DD /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	**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	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?	**Yes** ☐ **No** ☐

*If **no**, please select one relevant reason:*	
Concerned about worsening of seizures	☐
Forgotten to change dose	☐
Instructions not clear	☐

POSTNATAL FOLLOW-UP BOOKLET	Adherence checklist Part 2	Participant UTIN	Visit date
		__ __/__ __ __	__/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	
__/MMM/YY			µmol/l ☐	mg/l ☐
__/MMM/YY			µmol/l ☐	mg/l ☐
__/MMM/YY			µmol/l ☐	mg/l ☐
__/MMM/YY			µmol/l ☐	mg/l ☐
__/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		__/MMM/YYYY	Yes ☐ No ☐	__/MMM/YYYY
		__/MMM/YYYY	Yes ☐ No ☐	__/MMM/YYYY
		__/MMM/YYYY	Yes ☐ No ☐	__/MMM/YYYY
		__/MMM/YYYY	Yes ☐ No ☐	__/MMM/YYYY
		__/MMM/YYYY	Yes ☐ No ☐	__/MMM/YYYY
		__/MMM/YYYY	Yes ☐ No ☐	__/MMM/YYYY
		__/MMM/YYYY	Yes ☐ No ☐	__/MMM/YYYY

		DD /MMM /YYYY	Yes ☐ No ☐	DD /MMM /YYYY
		DD /MMM /YYYY	Yes ☐ No ☐	DD /MMM /YYYY

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)*	

8.8 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 ☐

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 ☐
DD / MMM / YYYY				µmol/l ☐ mg/l ☐

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

8.9 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		

APPENDIX 9 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: 020 7882 2525
Fax: 020 7882 2552

How do I use my EMPIRE diary?

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

- 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.

<u>What if I forget to update my diary?</u>

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".

<u>What if I have any questions?</u>

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)

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

APPENDIX 10 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: _____

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?

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	

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

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	