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## BMJ Paediatrics Open

**A PROSPECTIVE OBSERVATIONAL STUDY OF ADVERSE  
DRUG REACTIONS OF ANTIEPILEPTIC DRUGS IN CHILDREN  
IN THE UNITED KINGDOM**

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Manuscripts

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4 **A PROSPECTIVE OBSERVATIONAL STUDY OF ADVERSE DRUG**  
5 **REACTIONS OF ANTIEPILEPTIC DRUGS IN CHILDREN IN THE**  
6 **UNITED KINGDOM**  
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21 **WHAT IS ALREADY KNOWN**

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23 **Antiepileptic drugs (AEDs) have significant drug toxicity**

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25 **New AEDs are being more widely used**  
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30 **WHAT THIS STUDY HOPES TO ADD**

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32 **Comparative data regarding the safety profile of individual AEDs**

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34 **Discontinuation rates for individual AEDs**  
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## ABSTRACT

### Background

Epilepsy is a common chronic disease of children that can be treated with antiepileptic drugs (AEDs). AEDs, however, have significant side effects. Newer AEDs are thought to have fewer side effects. There have, however, been few comparative studies of AED toxicity. The aim is to compare the safety profile of the most frequently used AEDs by performing a multicentre prospective cohort study.

### Design

A multicentre prospective cohort study of children on AED drug treatment in hospitals across the United Kingdom. Ethical approval will be obtained.

### Sample size

Three thousand children on treatment for epilepsy will be recruited from paediatric clinics. It is expected that this sample size will have the potential to compare toxicity between the most frequently used AEDs.

**Duration of study** 24 months

### Outcome measure

Adverse drug reactions to antiepileptic drugs. These will be identified by the use of a validated questionnaire, the Paediatric Epilepsy Side Effect Questionnaire (PESQ).

### Discussion

Toxicity of individual AEDs when given as monotherapy and polytherapy will be determined. Additionally, discontinuation rates due to ADRs will be determined. The data will assist clinicians in choosing AEDs with the least toxicity.

## INTRODUCTION

Epilepsy is a widespread disorder affecting 0.5% children under 16 years old in the UK (1). Conventional (old) antiepileptic drugs (AEDs), which are AEDs in use before the early 1990s, are still generally preferred to the second generation AEDs in children in the UK (2). Lamotrigine is the most commonly prescribed new generation AED (0.55 subjects per 1,000 person-years) (2). A study of the UK General Practice Research Database (GPRD) showed a fivefold increase in the prevalence of newer AED prescription for children in 2005 (3). Over the 13 year period, there was a 17% decrease in conventional AED prescriptions with a corresponding increase in new AED prescriptions (3). This increase in the utilisation of new AEDs in children presents a fresh challenge of identifying new toxicities and new drug interactions.

AEDs are the most common cause of drug induced fatalities in children in the UK (4). A 10 year retrospective review of adverse drug reactions (ADRs) in children in the USA also identified AEDs as the third most common cause of ADRs (5). A report of ADRs in Swedish children over a 15 year period (1987-2001) showed that lamotrigine was the seventh most common cause of ADRs (6). According to a 2012 UK clinical audit for children with epilepsy, lack of sufficient information on side effects was identified as one of the most common areas for improvement in epilepsy care in children (7). Large pharmacovigilance studies of ADRs of AEDs in children are lacking. Most studies of toxicity of AEDs have focussed on a single AED (8-10).

There have been few prospective cohort studies of children with epilepsy on AEDs focussing on toxicity (11-13). These studies identified ADRs in 31-63% children receiving AEDs. The number of children in the studies ranged from 102 to 277, which is too small to compare the toxicity of the AEDs statistically. With the increasing use of new AEDs, there is a greater need to determine and compare the safety of these drugs, especially with the more established old generation drugs.

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3 RCTs are useful to compare effectiveness of AEDs. They are however, rarely, powered  
4 to look at toxicity (14) and toxicity is poorly described in RCTs (15). Additionally, RCTs  
5 of AEDs in children are uncommon. Most RCTs of AEDs involve adults and children, and  
6 the paediatric data are not usually reported separately (15). Discontinuation of an AED is  
7 due to either lack of effectiveness or toxicity. The discontinuation rate to toxicity has  
8 ranged from 2% to 30% for most AEDs (10, 12, 16-18).

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11 When comparative efficacies are similar, clinicians select AEDs based on their safety  
12 profile. Studies have shown that many of the newer AEDs do not have superior efficacy  
13 to the older drugs, and their relative safety, based on the available knowledge, is their  
14 only comparative advantage (19). Therefore, large pharmacovigilance studies are  
15 required to identify ADRs in children and adolescents.

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18 Only two validated questionnaires have been developed for AED ADRs in children. These  
19 are the Hague Side Effect Scale (HASES) (20) and the Paediatric Epilepsy Side Effect  
20 Questionnaire (PESQ) (21). PESQ is the more recent of the two and it was designed to  
21 address the shortcomings of the HASES which include: validation in a small sample size,  
22 validation only in patients with chronic epilepsy and not being representative of patients  
23 receiving new generation AEDs. For this study PESQ will be used to elicit ADRs.

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26 The aim is to perform a prospective cohort study of children on AEDs to determine the  
27 nature and rate of ADRs in this population.

### 28 29 30 **Primary objectives**

- 31 • To describe the incidence of ADRs in children receiving each AED
- 32 • To compare the safety profile of the most frequently used AEDs.
- 33 • To determine discontinuation rates for the most frequently used AEDs

## Secondary objectives

- To compare toxicity of individual AEDs when given as monotherapy and polytherapy
- To evaluate the preventability of ADRs in these children
- To determine the current prescription rates of AEDs in children
- To describe the effect of factors such as age, dose, polypharmacy and duration of treatment on toxicity of AEDs

## STUDY DESIGN

### Study configuration and population

This will be the first multicentre prospective cohort study of the safety of AEDs in children in the United Kingdom. The aim is to prospectively study 3000 children with epilepsy for ADRs. We aim to enrol a minimum of 500 children receiving valproic acid, carbamazepine, lamotrigine and levetiracetam, respectively, so as to compare the adverse effect profile of these drugs effectively. It is expected that this sample size will allow one to compare toxicity between the most frequently used AEDs. There will be no other intervention other than that obtained in routine practice in the respective hospitals. Information on ADRs will be extracted and recorded onto a case record form.

Paediatric patients receiving AED treatment will be recruited from hospital outpatient clinics over a period of 12 months. Enrolment shall start as soon as the REC and R&D approvals are obtained. The study will close at 24 months, after the last recruited patients have been followed up for the requisite minimum of 12 months.

Participants will be recruited from outpatient clinics and inpatients attending participating centres (Nottingham Children's Hospital, Derbyshire Children's hospital, Alder Hey Children's Hospital Liverpool, Newcastle Children's Hospital, Coventry Hospital and Kings Mill Hospital, Mansfield have all agreed to participate so far. It is hoped other centres will also join the study). All recruited children will be seen for follow-up in the hospitals



where treatment was initiated. In order to avoid selection bias, all eligible patients will be approached for inclusion into the study from general paediatric and epilepsy clinics. A member of the potential participant's usual care team will inform the potential participant and their parents or guardian about the details of the study – this may be directly at their usual clinic visit or by a letter from the team about the study, which includes the patient information sheet. This information will be appropriate for age and maturity of the participants, and if required, the usual hospital interpreter and translator services will be utilised. The participant information sheets, and consent forms, will only be available in English. Patients and their parents/guardian shall be informed that participation is voluntary and that they are free to withdraw from the study at any time. They shall also be informed that refusal to participate or withdrawal from the study will not affect the quality of care received. In the event of their withdrawal it will be explained that their data collected so far can be withdrawn and we will seek consent to use the data in the final analyses where appropriate.

### **Inclusion criteria**

- Paediatric patients with epilepsy aged 18 years or less
- Paediatric patients receiving one or more AEDs for epilepsy
- Patients whose parents/guardian have provided written informed consent or who have themselves (if 16 years old or over) signed a written informed consent to participate in the study.

### **Exclusion criteria**

- Unable or unwilling to give informed consent or withdrawal of consent
- Plans to relocate to an area not covered by the study

Study participants will be followed up for 12-18 months

### **Data collection**

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3 All relevant data will be recorded, by nominated member(s) of the research team, on a  
4 case report form (CRF). Each participant will have a CRF and be assigned a unique  
5 identification number.  
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### 8 9 10 11 12 **Baseline data**

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15 At entry into the study, the following baseline information will be recorded in the CRF:  
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- 17 • unique patient identification number
  - 18 • contact telephone number and/or email address
  - 19 • date of entry into the study
  - 20 • eligibility for study entry based on inclusion/exclusion criteria
  - 21 • age at study entry, in years and months
  - 22 • gender
  - 23 • weight and height
  - 24 • seizure type (e.g. generalised tonic clonic, absence, myoclonic, partial)
  - 25 • epilepsy syndrome (if identified); epilepsy category
  - 26 • cause of the epilepsy (if identified)
  - 27 • concomitant neurological disorder(s)
  - 28 • the age at diagnosis and duration of epilepsy
  - 29 • Seizure frequency recorded as average number of seizures per month in the  
30 preceding 3 months (for patients already on AEDs) or average number of seizures  
31 per month since presentation in newly diagnosed epileptics
  - 32 • current anticonvulsant(s) with doses and formulation
  - 33 • date of commencement of current AEDs
  - 34 • other medications
  - 35 • concurrent medical disorders
  - 36 • prior or current reported behavioural problems
  - 37 • first recognized seizure date.
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- Girls aged 10 years and over will also be asked whether they have received advice about contraception and possible effects of AEDs on pregnancy.

### **Follow-up data**

Follow-up data will be collected during regularly scheduled clinic visits (3 to 6 monthly). Relevant data will also be obtained after any unscheduled clinic visit. This information will be obtained from the participants' hospital notes. Important information to be collected at follow-up will include:

- date of the visit
- weight
- AEDs, their doses and formulation
- plasma concentrations of AEDs (if clinician has requested these and reason for requesting them)
- type of seizures since the last visit
- emergence of any new seizure types
- frequency of seizures, recorded as average number of seizures per month since last visit
- suspected ADRs since last visit
- a detailed record of any change to the drug regime
- reason for change in drug regime

All data on ADRs will be forwarded on to the chief investigator.

### **ADR surveillance**

Surveillance for ADRs will be carried out prospectively on all patients in the cohort by the clinician, researcher, parents/guardian and the patient. Patients will be followed up 3-6

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3 monthly for 12-18 months. If a patient experiences an ADR to one AED that results in a  
4 change in therapy, then the monitoring will continue for up to a maximum of 18 months.  
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8 ADRs will be detected by administering a validated questionnaire for ADRs (PESQ) to  
9 patients or their parents (22). During each of the follow-up visits, attending physicians  
10 will also ask parents/patients generally about the occurrence of any adverse reaction.  
11 ADR information from this general enquiry will be documented on a specifically designed  
12 form that will be kept in the patient's case notes. Patients will have a total of at least  
13 three follow-up visits.  
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20 At enrolment, participants will be asked if they wish to be contacted by email or by  
21 telephone. For participants who wish to be contacted by email, a three monthly email  
22 will be sent to parents/guardian or directly to the participant (if 16 years old or more).  
23 This will be sent by a nominated member of the research team. The email will include a  
24 link to the PESQ which the patients/parents will be required to fill anonymously (Table  
25 1). For participants or their parents/guardian who wish to be contacted by telephone,  
26 they will be contacted and questions regarding ADRs from the structured questionnaire  
27 (PESQ) will be asked. The attending physicians will be notified of any severe ADR  
28 indicated by the patients or parents on the PESQ.  
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39 Information from general ADR enquiry will be documented on a follow-up visit form by  
40 the attending physician during each follow-up visit. This will supplement all ADR  
41 information elicited specifically with the questionnaire. The clinical course of each  
42 suspected ADR will be followed until resolution or stabilisation. All prescription changes,  
43 interventions, laboratory findings and the time course relationship of the reaction to the  
44 medication will be documented. The progress of the ADR will be monitored in  
45 subsequent clinic visits to determine if it is unchanged, has resolved or worsened.  
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54 If AEDs are changed, a member of the research team will determine from the  
55 participant's notes the reason for the prescription change. If the reason for the change  
56 is not satisfactorily stated in the notes, a member of the research team may enquire  
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from the attending physician. In the event of a child experiencing an ADR, any relevant clinical blood tests will be performed if deemed necessary by the treating clinician and this may include determination of a drug level where applicable. In the event of a child experiencing an ADR, any relevant clinical blood tests will be performed if deemed necessary by the treating clinician and this will include determination of a drug level where applicable. The attending physician shall take all necessary steps to mitigate the ADR. This may include: discontinuation of the drug or any other concomitant drug or reduction in drug dosages. The participants and their parents/guardians will be fully informed of all the measures towards ameliorating the effect of the ADR.

**Table 1: The Paediatric Epilepsy Side Effect Questionnaire (PESQ)**

	Side effect related to seizure medicine	Not present (1)	Low Severity (2)	Low-moderate severity (3)	Moderate severity (4)	Moderate-high severity (5)	High severity (6)
1	Slow thinking						
2	Memory problems						
3	Confusion						
4	Poor school results						
5	Decreased concentration						
6	Attention difficulties						
7	Unstable walking						
8	Poor coordination, clumsiness						
9	Falling (not seizure)						
10	Speech difficulties						
11	Aggression						
12	Hyperactivity						
13	Personality change						
14	Drowsiness,						

	sleepiness						
15	Fatigue, tiredness						
16	Dizziness, lightheadedness						
17	Headaches						
18	Increase in appetite						
19	Weight gain						
20	Others						

### Evaluation and classification of suspected adverse drug reactions

All suspected ADRs will be assessed by a member of the research team, by using the Naranjo algorithm, which is a standardised causality assessment tool for suspected ADRs (9). This method has previously been used in paediatric ADR surveillance studies (11, 12).

All suspected ADRs will be evaluated and classified (13) as:

**Definite** - A clinical event or abnormal laboratory test finding that has a plausible time relationship to the drug and cannot be explained by disease or concomitant drug. There is usually a favourable response to drug withdrawal and recurrence on re-challenge. This ADR will have a Naranjo score of 9 or more.

**Probable** - A clinical event or abnormal laboratory test with a reasonable time course relationship to the administered drug and not due to other drug or concurrent disease. There is a reasonable favourable response on withdrawal. This will have a Naranjo score of 5 to 8.

**Possible** - A clinical event or abnormal laboratory finding with a reasonable time course relationship to the drug but could also be explained by a concomitant drug or a concurrent illness. This will have a Naranjo score of 1 to 4.

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3 **Not related** – No possible relationship (i.e., the temporal relationship between  
4 treatment exposure and the adverse event onset/course is unreasonable or  
5 incompatible; or a causal relationship to study treatment is implausible). This will have  
6 a Naranjo score of <1.  
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11 The severity of ADRs will be classified in accordance with previously used method (22,  
12 23)  
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- 14 1. **Severe** - fatal or potentially life threatening.
- 15 16 2. **Moderate** – requiring treatment or prolonging the length of stay in hospital.
- 17 18 3. **Mild** – no treatment required and no effect on length of stay in hospital.

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21 Severe ADRs will be reported to the Committee on Safety of Medicines (CSM).  
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25 The preventability of ADRs will be assessed using the Schumock and Thornton scale  
26 (24). This scale, which has been used previously in another AED pharmacovigilance  
27 study (12) classifies the preventability of ADRs into: definitely preventable, probably  
28 preventable and not preventable, based on conformity with a set of criteria.  
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### 39 **Statistics**

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41 The primary outcome will be the incidence of ADRs for each of the prescribed AED.  
42 Using Chi<sup>2</sup> analysis, and Fischer's exact test when appropriate, ADRs and discontinuation  
43 rates of individual AEDs will be compared.  
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49 Secondary outcomes will be the effects of polytherapy and monotherapy on ADRs and  
50 discontinuation rates. Chi<sup>2</sup> analysis, and Fischer's exact test when appropriate will be  
51 used. Other secondary outcomes such as the association between age and type of  
52 epilepsy with ADR will be analysed using one way ANOVA. Multivariate logistic  
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3 regression will be used to determine the predictors of ADRs in children receiving AEDs.  
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5 Excel and SPSS will be used for statistical analyses.  
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### 8 9 10 **Ethics and dissemination**

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13 The study will only be initiated after the protocol, consent form and the participants'  
14 information sheet are approved by the Research Ethics Committee (REC), and the  
15 respective National Health Service (NHS) Research & Development (R&D) departments.  
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17 If an amendment to the protocol requiring REC approval is necessary, such amendments  
18 will not be effected until revised informed consent forms and participant information  
19 sheets are reviewed and approved by the R&D departments and the REC. Should the  
20 amendment be intended to prevent a clear immediate hazard to participants, such  
21 amendment may be effected, provided that the REC are notified as soon as possible and  
22 an approval is requested. Minor protocol amendments only for logistical or  
23 administrative changes may be implemented immediately; and the REC will be informed.  
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27 The study will be conducted in compliance with the principles of: Good Clinical Practice,  
28 the Department of Health Research Governance Framework for Health and Social Care,  
29 2005, and in accordance with the 1996 Helsinki declaration.  
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### 32 33 34 **Informed consent**

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37 Written informed consent will be obtained from parents/guardian of potential participants  
38 less than 16 years old, at the time of clinic appointment. Written consent will be sought  
39 directly from patients 16 years old or over. If a participant turns 16 years old during the  
40 course of the study, consent will be sought from the participant in order to continue  
41 participation in the study. The investigator will explain the details of the study and  
42 provide age appropriate participant information sheet to the participants and their  
43 parents/guardian. All questions about the study, by either the patient and or the  
44 parent/guardian, will be answered by the investigator. Participants will be allowed  
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3 sufficient time to decide whether to participate in the study or not. Before enrolment  
4 into the study, the consent form will be signed by parents/guardian, or by the participant  
5 if aged 16 years or more. If either the potential participant or their parent/guardian  
6 decline to consent, or if under 16 years of age the child or young person declines to be  
7 included, they will not enter the study.  
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12 The participant or their parent/guardian will keep a copy of the consent form, while the  
13 original copy will be kept by the chief investigator in the recruitment file, a third copy will  
14 be kept in the patient's hospital record. In the event of a significant protocol change, a  
15 fresh signed written consent will be sought from participants, parents or guardians and  
16 the revised document will be submitted to the REC and the sites' R&D for approval.  
17 Assent will be sought from any patient considered mature enough to comprehend the  
18 importance of the study.  
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### 31 **Discontinuation of study participation**

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33 Participants may choose to withdraw from the study, on their own or on the request of  
34 their parents/guardian, at any time during the course of the study. Subjects may  
35 withdraw for any reason without prejudice to his/her future medical care by the  
36 physician or at the institution. Upon withdrawal of consent, the date and reason for  
37 consent withdrawal will be documented. Participants data collected up to the date of the  
38 withdrawal of consent may be included in the final analysis. The investigator may also  
39 choose to withdraw a participant from the study if such person is lost to follow up, has  
40 moved out of the study area, does not comply with treatment or for any other practical  
41 reason that may affect the integrity of the study. Withdrawn participants will not be  
42 replaced.  
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## Study records and data management

### Case report forms (CRF)

Each participant will be assigned a unique study Patient Identification Number, for use on CRFs, other study documents and the electronic database. CRFs will be treated as confidential documents and held securely in accordance with regulations. The investigator will make a separate confidential record of the participant's name, date of birth, local hospital number or NHS number, and Patient Identification Number, to permit identification of all participants enrolled in the study, in case additional follow-up is required.

CRFs shall be restricted to those personnel approved by the Chief Investigator and recorded as such in the study records.

All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but not obliterated by using correction fluid and the correction inserted, initialled and dated.

The Chief Investigator shall sign a declaration ensuring accuracy of data recorded in the CRF.

### Record retention and archiving

The Chief Investigator will retain all records and documents pertaining to the study for 7 years in compliance with the ICH/GCP guidelines and the University of Nottingham Code of Research Conduct and Research Ethics. If the responsible investigator can no longer retain these records, another person will be nominated for this purpose.

The final archiving of the study documents and databases (and associated meta-encryption codes) held by the Chief Investigator shall be at the secure archive facility at the University of Nottingham.

### **Publication and dissemination policy**

Participants will not be paid to participate in the study. There will be no hospital visits in excess of usual care.

Findings will be published in peer review journals.

### **REFERENCES**

1. Joint Epilepsy Council of the UK and Ireland. Epilepsy prevalence, incidence and other statistics 2011 [20/01/2014]. Available from: [http://www.epilepsyscotland.org.uk/pdf/Joint\\_Epilepsy\\_Council\\_Prevalence\\_and\\_Incidence\\_September\\_11\\_\(3\).pdf](http://www.epilepsyscotland.org.uk/pdf/Joint_Epilepsy_Council_Prevalence_and_Incidence_September_11_(3).pdf).
2. Hsia Y, Neubert A, Sturkenboom MC, Murray ML, Verhamme K, Sen F, et al. Comparison of antiepileptic drug prescribing in children in three European countries. *Epilepsia*. 2010;51(5):789-96.
3. Ackers R, Murray ML, Besag F, Wong IC. Prioritizing children's medicines for research: a pharmacoepidemiological study of antiepileptic drugs. *Br J Clin Pharmacol*. 2007;63(6):689-97.
4. Clarkson A, Choonara I. Surveillance for fatal suspected adverse drug reactions in the UK. *Arch Dis Child*. 2002;87(6):462-6.
5. Le J, Nguyen T, Law AV, Hodding J. Adverse drug reactions among children over a 10-year period. *Pediatrics*. 2006;118(2):555-62.
6. Kimland E, Rane A, Ufer M, Panagiotidis G. Paediatric adverse drug reactions reported in Sweden from 1987 to 2001. *Pharmacoepidemiol Drug Safety*. 2005;14(7):493-9.
7. Royal College of Paediatrics and Child Health. United Kingdom collaborative clinical audit of health care for children and young people with suspected epileptic seizures 2012:[1-118 pp.]. Available from: [http://www.rcpch.ac.uk/system/files/protected/page/Epilepsy\\_web.pdf](http://www.rcpch.ac.uk/system/files/protected/page/Epilepsy_web.pdf).
8. Aurich-Barrera B, Wilton L, Brown D, Shakir S. Paediatric Postmarketing Pharmacovigilance Using Prescription-Event Monitoring. *Drug Saf*. 2010;33(9):751-63.

9. Aurich-Barrera B, Wilton L, Brown D, Shakir S. Paediatric post-marketing pharmacovigilance: comparison of the adverse event profile of vigabatrin prescribed to children and adults. *Pharmacoepidemiol Drug Safety*. 2011;20(6):608-18.
10. Egunsola O, Choonara I, Sammons HM. Safety of lamotrigine in paediatrics: a systematic review. *BMJ Open* 2015; 5: e007711.
11. Anderson M, Egunsola O, Cherrill J, Millward C, Fakis A, Choonara I. A prospective study of adverse drug reactions to antiepileptic drugs in children *BMJ Open*. 2015;5(6):e008298.
12. Bansal D, Azad C, Kaur M, Rudroju N, Vepa P, Guglani V. Adverse effects of antiepileptic drugs in North Indian pediatric outpatients. *Clin Neuropharmacol*. 2013;36(4):107-13.
13. Choonara I. Anticonvulsant toxicity in paediatric out-patients. *The Br J Clin Practice*. 1988;42(1):21.
14. Makuch RW. Detecting rare adverse events in postmarketing studies: sample size considerations. *Drug Information Journal*. 2006;40(1):89-98.
15. Anderson M, Choonara I. A systematic review of safety monitoring and drug toxicity in published randomised controlled trials of antiepileptic drugs in children over a 10-year period. *Arch Dis Child*. 2010;95(9):731-8.
16. Egunsola O, Choonara I, Sammons HM. Safety of levetiracetam in paediatrics: a systematic review. *PLoS One* 2016; 11 :e0149686.
17. Dudley RW, Penney SJ, Buckley DJ. First-drug treatment failures in children newly diagnosed with epilepsy. *Pediatr Neurol*. 2009;40(2):71-7.
18. De Silva M, MacArdle B, McGowan M, Hughes E, Stewart J, Reynolds E, et al. Randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed childhood epilepsy. *Lancet*. 1996;347(9003):709-13.
19. Guerrini R, Zaccara G, la Marca G, Rosati A. Safety and tolerability of antiepileptic drug treatment in children with epilepsy. *Drug Saf*. 2012;35(7):519-33.
20. Carpay HA, Arts WF, Vermeulen J, Stroink H, Brouwer OF, Boudewyn Peters A, et al. Parent-completed scales for measuring seizure severity and severity of side-effects of antiepileptic drugs in childhood epilepsy: development and psychometric analysis. *Epilepsy Res*. 1996;24(3):173-81.
21. Morita DA, Glauser TA, Modi AC. Development and validation of the pediatric epilepsy side effects questionnaire. *Neurology*. 2012;79(12):1252-8.
22. Marson AG, Appleton R, Baker G, Chadwick D, Doughty J, Eaton B, et al. A Randomised Controlled Trial Examining the Longer-term Outcomes of Standard Versus New Antiepileptic Drugs: The SANAD Trial: National Co-ordinating Centre for Health Technology Assessment; 2007.
23. Biton V, Edwards KR, Montouris GD, Sackellares JC, Harden CL, Kamin M. Topiramate titration and tolerability. *Ann Pharmacother*. 2001;35(2):173-9.
24. Schumock G, Thornton J. Focusing on the preventability of adverse drug reactions. *Hospital Pharmacy*. 1992;27(6):538.

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## BMJ Paediatrics Open

**A PROSPECTIVE OBSERVATIONAL STUDY OF ADVERSE  
DRUG REACTIONS OF ANTIEPILEPTIC DRUGS IN CHILDREN  
IN THE UNITED KINGDOM**

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Manuscripts

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4 **A PROTOCOL FOR A PROSPECTIVE OBSERVATIONAL STUDY OF**  
5 **ADVERSE DRUG REACTIONS OF ANTIEPILEPTIC DRUGS IN**  
6 **CHILDREN IN THE UNITED KINGDOM**  
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21 **WHAT IS ALREADY KNOWN**

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23 **Antiepileptic drugs (AEDs) have significant drug toxicity**

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25 **New AEDs are being more widely used**  
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30 **WHAT THIS STUDY HOPES TO ADD**

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32 **Comparative data regarding the safety profile of individual AEDs**

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34 **Discontinuation rates for individual AEDs**  
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## ABSTRACT

### Background

Epilepsy is a common chronic disease of children that can be treated with antiepileptic drugs (AEDs). AEDs, however, have significant side effects. Newer AEDs are thought to have fewer side effects. There have, however, been few comparative studies of AED toxicity. The aim is to compare the safety profile of the most frequently used AEDs by performing a multicentre prospective cohort study. This protocol describes the planned study.

### Design

A multicentre prospective cohort study of children on AED drug treatment in hospitals across the United Kingdom. Ethical approval will be obtained.

### Sample size

Three thousand children on treatment for epilepsy will be recruited from paediatric clinics. It is expected that this sample size will have the potential to compare toxicity between the most frequently used AEDs.

**Duration of study** 24 months

### Outcome measure

Adverse drug reactions to antiepileptic drugs. These will be identified by the use of a validated questionnaire, the Paediatric Epilepsy Side Effect Questionnaire (PESQ). They will be evaluated using the Naranjo algorithm. Preventability will be assessed using the Schumock and Thornton scale.

### Discussion

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3 Toxicity of individual AEDs when given as monotherapy and polytherapy will be  
4 determined. Additionally, discontinuation rates due to ADRs will be determined. The  
5 data will assist clinicians in choosing AEDs with the least toxicity.  
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## 10 11 12 **INTRODUCTION**

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15 Epilepsy is a widespread disorder affecting 0.5% children under 16 years old in the UK  
16 (1). Conventional (old) antiepileptic drugs (AEDs), which are AEDs in use before the  
17 early 1990s, are still generally preferred to the second generation AEDs in children in the  
18 UK (2). Lamotrigine is the most commonly prescribed new generation AED (0.55  
19 subjects per 1,000 person-years) (2). A study of the UK General Practice Research  
20 Database (GPRD) showed a fivefold increase in the prevalence of newer AED prescription  
21 for children in 2005 (3). Over the 13 year period, there was a 17% decrease in  
22 conventional AED prescriptions with a corresponding increase in new AED prescriptions  
23 (3). This increase in the utilisation of new AEDs in children presents a fresh challenge of  
24 identifying new toxicities and new drug interactions.  
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36 AEDs are the most common cause of drug induced fatalities in children in the UK (4). A  
37 10 year retrospective review of adverse drug reactions (ADRs) in children in the USA  
38 also identified AEDs as the third most common cause of ADRs (5). A report of ADRs in  
39 Swedish children over a 15 year period (1987-2001) showed that lamotrigine was the  
40 seventh most common cause of ADRs (6). According to a 2012 UK clinical audit for  
41 children with epilepsy, lack of sufficient information on side effects was identified as one  
42 of the most common areas for improvement in epilepsy care in children (7). Large  
43 pharmacovigilance studies of ADRs of AEDs in children are lacking. Most studies of  
44 toxicity of AEDs have focussed on a single AED (8-10).  
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55 There have been few prospective cohort studies of children with epilepsy on AEDs  
56 focussing on toxicity (11-13). These studies identified ADRs in 31-63% children  
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3 receiving AEDs. The number of children in the studies ranged from 102 to 277, which is  
4 too small to compare the toxicity of the AEDs statistically. With the increasing use of  
5 new AEDs, there is a greater need to determine and compare the safety of these drugs,  
6 especially with the more established old generation drugs.  
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11 RCTs are useful to compare effectiveness of AEDs. They are however, rarely, powered  
12 to look at toxicity (14) and toxicity is poorly described in RCTs (15). Additionally, RCTs  
13 of AEDs in children are uncommon. Most RCTs of AEDs involve adults and children, and  
14 the paediatric data are not usually reported separately (15). Discontinuation of an AED is  
15 due to either lack of effectiveness or toxicity. The discontinuation rate to toxicity has  
16 ranged from 2% to 30% for most AEDs (10, 12, 16-18).  
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21 When comparative efficacies are similar, clinicians select AEDs based on their safety  
22 profile. Studies have shown that many of the newer AEDs do not have superior efficacy  
23 to the older drugs, and their relative safety, based on the available knowledge, is their  
24 only comparative advantage (19). Therefore, large pharmacovigilance studies are  
25 required to identify ADRs in children and adolescents.  
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34 Only two validated questionnaires have been developed for AED ADRs in children. These  
35 are the Hague Side Effect Scale (HASES) (20) and the Paediatric Epilepsy Side Effect  
36 Questionnaire (PESQ) (21). PESQ is the more recent of the two and it was designed to  
37 address the shortcomings of the HASES which include: validation in a small sample size,  
38 validation only in patients with chronic epilepsy and not being representative of patients  
39 receiving new generation AEDs. For this study PESQ will be used to elicit ADRs. There  
40 have been no prospective national multicentre studies of AED toxicity in children.  
41 Additionally, many of the single centre studies have not utilised either HASES or PESQ.  
42 This study will provide an excellent opportunity to use and evaluate the value of PESQ in  
43 determining the extent of AED toxicity in children.  
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55 The aim is to perform a prospective cohort study of children on AEDs to determine the  
56 nature and rate of ADRs in this population.  
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### Primary objectives

- To describe the incidence of ADRs in children receiving each AED
- To compare the safety profile of the most frequently used AEDs.
- To determine discontinuation rates for the most frequently used AEDs

### Secondary objectives

- To compare toxicity of individual AEDs when given as monotherapy and polytherapy
- To evaluate the preventability of ADRs in these children
- To determine the current prescription rates of AEDs in children
- To describe the effect of factors such as age, dose, polypharmacy and duration of treatment on toxicity of AEDs

## STUDY DESIGN

### Study configuration and population

This protocol is for the first multicentre prospective cohort study of the safety of AEDs in children in the United Kingdom. The aim is to prospectively study 3000 children with epilepsy for ADRs. We aim to enrol a minimum of 500 children receiving valproic acid, carbamazepine, lamotrigine and levetiracetam, respectively, so as to compare the adverse effect profile of these drugs effectively. It is expected that this sample size will allow one to compare toxicity between the most frequently used AEDs. There will be no other intervention other than that obtained in routine practice in the respective hospitals. Information on ADRs will be extracted and recorded onto a case record form.

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3 Paediatric patients receiving AED treatment will be recruited from hospital outpatient  
4 clinics over a period of 12 months. Enrolment shall start as soon as the REC and R&D  
5 approvals are obtained. The study will close at 24 months, after the last recruited  
6 patients have been followed up for the requisite minimum of 12 months.  
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11 Participants will be recruited from outpatient clinics and inpatients attending participating  
12 centres (Nottingham Children's Hospital, Derbyshire Children's hospital, Alder Hey  
13 Children's Hospital Liverpool, Newcastle Children's Hospital, Coventry Hospital and Kings  
14 Mill Hospital, Mansfield have all agreed to participate so far. It is hoped other centres  
15 will also join the study). All recruited children will be seen for follow-up in the hospitals  
16 where treatment was initiated. In order to avoid selection bias, all eligible patients will  
17 be approached for inclusion into the study from general paediatric and epilepsy clinics. A  
18 member of the potential participant's usual care team will inform the potential  
19 participant and their parents or guardian about the details of the study – this may be  
20 directly at their usual clinic visit or by a letter from the team about the study, which  
21 includes the patient information sheet. This information will be appropriate for age and  
22 maturity of the participants, and if required, the usual hospital interpreter and translator  
23 services will be utilised. The participant information sheets, and consent forms, will only  
24 be available in English. Patients and their parents/guardian shall be informed that  
25 participation is voluntary and that they are free to withdraw from the study at any time.  
26 They shall also be informed that refusal to participate or withdrawal from the study will  
27 not affect the quality of care received. In the event of their withdrawal it will be  
28 explained that their data collected so far can be withdrawn and we will seek consent to  
29 use the data in the final analyses where appropriate.  
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#### 49 **Inclusion criteria**

- 50 • Paediatric patients with epilepsy aged 18 years or less
  - 51 • Paediatric patients receiving one or more AEDs for epilepsy
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- Patients whose parents/guardian have provided written informed consent or who have themselves (if 16 years old or over) signed a written informed consent to participate in the study.

### **Exclusion criteria**

- Unable or unwilling to give informed consent or withdrawal of consent
- Plans to relocate to an area not covered by the study

Study participants will be followed up for 12-18 months

### **Data collection**

All relevant data will be recorded, by nominated member(s) of the research team, on a case report form (CRF). Each participant will have a CRF and be assigned a unique identification number.

### **Baseline data**

At entry into the study, the following baseline information will be recorded in the CRF:

- unique patient identification number
- contact telephone number and/or email address
- date of entry into the study
- eligibility for study entry based on inclusion/exclusion criteria
- age at study entry, in years and months
- gender
- weight and height
- seizure type (e.g. generalised tonic clonic, absence, myoclonic, partial)
- epilepsy syndrome (if identified); epilepsy category

- cause of the epilepsy (if identified)
- concomitant neurological disorder(s)
- the age at diagnosis and duration of epilepsy
- Seizure frequency recorded as average number of seizures per month in the preceding 3 months (for patients already on AEDs) or average number of seizures per month since presentation in newly diagnosed epileptics
- current anticonvulsant(s) with doses and formulation
- date of commencement of current AEDs
- other medications
- concurrent medical disorders
- prior or current reported behavioural problems
- first recognized seizure date.
- Girls aged 10 years and over will also be asked whether they have received advice about contraception and possible effects of AEDs on pregnancy.

#### **Follow-up data**

Follow-up data will be collected during regularly scheduled clinic visits (3 to 6 monthly). Relevant data will also be obtained after any unscheduled clinic visit. This information will be obtained from the participants' hospital notes. Important information to be collected at follow-up will include:

- date of the visit
- weight
- AEDs, their doses and formulation
- plasma concentrations of AEDs (if clinician has requested these and reason for requesting them)
- type of seizures since the last visit
- emergence of any new seizure types

- frequency of seizures, recorded as average number of seizures per month since last visit
- suspected ADRs since last visit
- a detailed record of any change to the drug regime
- reason for change in drug regime

All data on ADRs will be forwarded on to the chief investigator.

### **Outcome evaluation**

The main outcomes are ADRs. The methods utilised to detect the ADRs and their evaluation and classification are described below.

### **ADR surveillance**

Surveillance for ADRs will be carried out prospectively on all patients in the cohort by the clinician, researcher, parents/guardian and the patient. Patients will be followed up 3-6 monthly for 12-18 months. If a patient experiences an ADR to one AED that results in a change in therapy, then the monitoring will continue for up to a maximum of 18 months.

ADRs will be detected by administering a validated questionnaire for ADRs (PESQ) to patients or their parents (22). Only ADRs occurring within the preceding 3 months of enrolment will be recorded. During each of the follow-up visits, attending physicians will also ask parents/patients generally about the occurrence of any adverse reaction. ADR information from this general enquiry will be documented on a specifically designed form that will be kept in the patient's case notes. Patients will have a total of at least three follow-up visits. The follow up visits will ensure that transient self-correcting ADRs are distinguished from more clinically significant ADRs.



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3 At enrolment, participants will be asked if they wish to be contacted by email or by  
4 telephone. For participants who wish to be contacted by email, a three monthly email  
5 will be sent to parents/guardian or directly to the participant (if 16 years old or more).  
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7 This will be sent by a nominated member of the research team. The email will include a  
8 link to the PESQ which the patients/parents will be required to fill anonymously (Table  
9 1). For participants or their parents/guardian who wish to be contacted by telephone,  
10 they will be contacted and questions regarding ADRs from the structured questionnaire  
11 (PESQ) will be asked. The attending physicians will be notified of any severe ADR  
12 indicated by the patients or parents on the PESQ.  
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21 Information from general ADR enquiry will be documented on a follow-up visit form by  
22 the attending physician during each follow-up visit. This will supplement all ADR  
23 information elicited specifically with the questionnaire. The clinical course of each  
24 suspected ADR will be followed until resolution or stabilisation. All prescription changes,  
25 interventions, laboratory findings and the time course relationship of the reaction to the  
26 medication will be documented. The progress of the ADR will be monitored in  
27 subsequent clinic visits to determine if it is unchanged, has resolved or worsened.  
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36 If AEDs are changed, a member of the research team will determine from the  
37 participant's notes the reason for the prescription change. If the reason for the change  
38 is not satisfactorily stated in the notes, a member of the research team may enquire  
39 from the attending physician. In the event of a child experiencing an ADR, any relevant  
40 clinical blood tests will be performed if deemed necessary by the treating clinician and  
41 this may include determination of a drug level where applicable. In the event of a child  
42 experiencing an ADR, any relevant clinical blood tests will be performed if deemed  
43 necessary by the treating clinician and this will include determination of a drug level  
44 where applicable. The attending physician shall take all necessary steps to mitigate the  
45 ADR. This may include: discontinuation of the drug or any other concomitant drug or  
46 reduction in drug dosages. The participants and their parents/guardians will be fully  
47 informed of all the measures towards ameliorating the effect of the ADR.  
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**Table 1: The Paediatric Epilepsy Side Effect Questionnaire (PESQ)**

	Side effect related to seizure medicine	Not present (1)	Low Severity (2)	Low-moderate severity (3)	Moderate severity (4)	Moderate-high severity (5)	High severity (6)
1	Slow thinking						
2	Memory problems						
3	Confusion						
4	Poor school results						
5	Decreased concentration						
6	Attention difficulties						
7	Unstable walking						
8	Poor coordination, clumsiness						
9	Falling (not seizure)						
10	Speech difficulties						
11	Aggression						
12	Hyperactivity						
13	Personality change						
14	Drowsiness, sleepiness						
15	Fatigue, tiredness						
16	Dizziness, lightheadedness						
17	Headaches						
18	Increase in appetite						
19	Weight gain						
20	Others						

**Evaluation and classification of suspected adverse drug reactions**

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3 All suspected ADRs will be assessed by a member of the research team, by using the  
4 Naranjo algorithm, which is a standardised causality assessment tool for suspected ADRs  
5 (9). This method has previously been used in paediatric ADR surveillance studies (11,  
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7 12).

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10 All suspected ADRs will be evaluated and classified (13) as:

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14 **Definite** - A clinical event or abnormal laboratory test finding that has a plausible time  
15 relationship to the drug and cannot be explained by disease or concomitant drug. There  
16 is usually a favourable response to drug withdrawal and recurrence on re-challenge.  
17 This ADR will have a Naranjo score of 9 or more.

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23 **Probable** - A clinical event or abnormal laboratory test with a reasonable time course  
24 relationship to the administered drug and not due to other drug or concurrent disease.  
25 There is a reasonable favourable response on withdrawal. This will have a Naranjo score  
26 of 5 to 8.

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32 **Possible** - A clinical event or abnormal laboratory finding with a reasonable time course  
33 relationship to the drug but could also be explained by a concomitant drug or a  
34 concurrent illness. This will have a Naranjo score of 1 to 4.

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45 **Not related** - No possible relationship (i.e., the temporal relationship between  
46 treatment exposure and the adverse event onset/course is unreasonable or  
47 incompatible; or a causal relationship to study treatment is implausible). This will have  
48 a Naranjo score of <1.

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60 ADRs considered to be unrelated to treatment will not be included in the analysis of  
incidence rates and will not be included when comparing toxicity. All other ADRs  
(definite, probable and possible) will be combined together when comparing toxicity.

The severity of ADRs will be classified in accordance with previously used method (22,  
23)

1. **Severe** - fatal or potentially life threatening.
2. **Moderate** – requiring treatment or prolonging the length of stay in hospital.
3. **Mild** – no treatment required and no effect on length of stay in hospital.

Severe ADRs will be reported to the Committee on Safety of Medicines (CSM).

### **Calculation of incidence of ADRs and discontinuation rates**

The most valuable comparative data will be from patients who are receiving monotherapy. The incidence rate for specific ADRs in relation to a specific AED will be calculated by dividing the number of cases of the ADR occurring while on treatment with the number of children receiving the AED. The duration of treatment with the AED will be utilised to calculate the incidence of the ADR in relation to time. An incidence rate per child per year will be calculated. Discontinuation rates will be calculated by dividing the number of children who terminated treatment with an AED due to toxicity, divided by the number of children who received the drug.

### **Preventability of ADRs**

The preventability of ADRs will be assessed using the Schumock and Thornton scale (24). This scale, which has been used previously in another AED pharmacovigilance study (12) evaluates the preventability of ADRs based on a set of seven questions. These questions cover the appropriateness of the medicine; the dose, route and frequency of administration; therapeutic drug monitoring and serum concentrations (if appropriate); allergy; drug interactions and adherence.

### **Statistics**

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3 The primary outcome will be the incidence of ADRs for each of the prescribed AED.  
4 Using Chi<sup>2</sup> analysis, and Fischer's exact test when appropriate, ADRs and discontinuation  
5 rates of individual AEDs will be compared.  
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10 Secondary outcomes will be the effects of polytherapy and monotherapy on ADRs and  
11 discontinuation rates. Chi<sup>2</sup> analysis, and Fischer's exact test when appropriate will be  
12 used. Other secondary outcomes such as the association between age and type of  
13 epilepsy with ADR will be analysed using one way ANOVA. Multivariate logistic  
14 regression will be used to determine the predictors of ADRs in children receiving AEDs.  
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Excel and SPSS will be used for statistical analyses.

### **Ethics and dissemination**

The study will only be initiated after the protocol, consent form and the participants' information sheet are approved by the Research Ethics Committee (REC), and the respective National Health Service (NHS) Research & Development (R&D) departments. If an amendment to the protocol requiring REC approval is necessary, such amendments will not be effected until revised informed consent forms and participant information sheets are reviewed and approved by the R&D departments and the REC. Should the amendment be intended to prevent a clear immediate hazard to participants, such amendment may be effected, provided that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for logistical or administrative changes may be implemented immediately; and the REC will be informed.

The study will be conducted in compliance with the principles of: Good Clinical Practice, the Department of Health Research Governance Framework for Health and Social Care, 2005, and in accordance with the 1996 Helsinki declaration.

### **Informed consent**

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3 Written informed consent will be obtained from parents/guardian of potential participants  
4 less than 16 years old, at the time of clinic appointment. Written consent will be sought  
5 directly from patients 16 years old or over. If a participant turns 16 years old during the  
6 course of the study, consent will be sought from the participant in order to continue  
7 participation in the study. The investigator will explain the details of the study and  
8 provide age appropriate participant information sheet to the participants and their  
9 parents/guardian. All questions about the study, by either the patient and or the  
10 parent/guardian, will be answered by the investigator. Participants will be allowed  
11 sufficient time to decide whether to participate in the study or not. Before enrolment  
12 into the study, the consent form will be signed by parents/guardian, or by the participant  
13 if aged 16 years or more. If either the potential participant or their parent/guardian  
14 decline to consent, or if under 16 years of age the child or young person declines to be  
15 included, they will not enter the study.  
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29 The participant or their parent/guardian will keep a copy of the consent form, while the  
30 original copy will be kept by the chief investigator in the recruitment file, a third copy will  
31 be kept in the patient's hospital record. In the event of a significant protocol change, a  
32 fresh signed written consent will be sought from participants, parents or guardians and  
33 the revised document will be submitted to the REC and the sites' R&D for approval.  
34 Assent will be sought from any patient considered mature enough to comprehend the  
35 importance of the study.  
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#### 47 **Discontinuation of study participation**

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49 Participants may choose to withdraw from the study, on their own or on the request of  
50 their parents/guardian, at any time during the course of the study. Subjects may  
51 withdraw for any reason without prejudice to his/her future medical care by the  
52 physician or at the institution. Upon withdrawal of consent, the date and reason for  
53 consent withdrawal will be documented. Participants data collected up to the date of the  
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3 withdrawal of consent may be included in the final analysis. The investigator may also  
4 choose to withdraw a participant from the study if such person is lost to follow up, has  
5 moved out of the study area, does not comply with treatment or for any other practical  
6 reason that may affect the integrity of the study. Withdrawn participants will not be  
7 replaced.  
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## 22 **Study records and data management**

### 23 **Case report forms (CRF)**

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27 Each participant will be assigned a unique study Patient Identification Number, for use  
28 on CRFs, other study documents and the electronic database. CRFs will be treated as  
29 confidential documents and held securely in accordance with regulations. The  
30 investigator will make a separate confidential record of the participant's name, date of  
31 birth, local hospital number or NHS number, and Patient Identification Number, to permit  
32 identification of all participants enrolled in the study, in case additional follow-up is  
33 required.  
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42 CRFs shall be restricted to those personnel approved by the Chief Investigator and  
43 recorded as such in the study records.  
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46 All paper forms shall be filled in using black ballpoint pen. Errors shall be lined out but  
47 not obliterated by using correction fluid and the correction inserted, initialled and dated.  
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51 The Chief Investigator shall sign a declaration ensuring accuracy of data recorded in the  
52 CRF.  
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## Record retention and archiving

The Chief Investigator will retain all records and documents pertaining to the study for 7 years in compliance with the ICH/GCP guidelines and the University of Nottingham Code of Research Conduct and Research Ethics. If the responsible investigator can no longer retain these records, another person will be nominated for this purpose.

The final archiving of the study documents and databases (and associated meta-encryption codes) held by the Chief Investigator shall be at the secure archive facility at the University of Nottingham.

## Publication and dissemination policy

Participants will not be paid to participate in the study. There will be no hospital visits in excess of usual care.

Findings will be published in peer review journals.

## REFERENCES

1. Joint Epilepsy Council of the UK and Ireland. Epilepsy prevalence, incidence and other statistics 2011 [20/01/2014]. Available from: [http://www.epilepsyscotland.org.uk/pdf/Joint\\_Epilepsy\\_Council\\_Prevalence\\_and\\_Incidence\\_September\\_11\\_\(3\).pdf](http://www.epilepsyscotland.org.uk/pdf/Joint_Epilepsy_Council_Prevalence_and_Incidence_September_11_(3).pdf).
2. Hsia Y, Neubert A, Sturkenboom MC, Murray ML, Verhamme K, Sen F, et al. Comparison of antiepileptic drug prescribing in children in three European countries. *Epilepsia*. 2010;51(5):789-96.
3. Ackers R, Murray ML, Besag F, Wong IC. Prioritizing children's medicines for research: a pharmacoepidemiological study of antiepileptic drugs. *Br J Clin Pharmacol*. 2007;63(6):689-97.
4. Clarkson A, Choonara I. Surveillance for fatal suspected adverse drug reactions in the UK. *Arch Dis Child*. 2002;87(6):462-6.
5. Le J, Nguyen T, Law AV, Hodding J. Adverse drug reactions among children over a 10-year period. *Pediatrics*. 2006;118(2):555-62.



6. Kimland E, Rane A, Ufer M, Panagiotidis G. Paediatric adverse drug reactions reported in Sweden from 1987 to 2001. *Pharmacoepidemiol Drug Safety*. 2005;14(7):493-9.
7. Royal College of Paediatrics and Child Health. United Kingdom collaborative clinical audit of health care for children and young people with suspected epileptic seizures 2012:[1-118 pp.]. Available from: [http://www.rcpch.ac.uk/system/files/protected/page/Epilepsy\\_web.pdf](http://www.rcpch.ac.uk/system/files/protected/page/Epilepsy_web.pdf).
8. Aurich-Barrera B, Wilton L, Brown D, Shakir S. Paediatric Postmarketing Pharmacovigilance Using Prescription-Event Monitoring. *Drug Saf*. 2010;33(9):751-63.
9. Aurich-Barrera B, Wilton L, Brown D, Shakir S. Paediatric post-marketing pharmacovigilance: comparison of the adverse event profile of vigabatrin prescribed to children and adults. *Pharmacoepidemiol Drug Safety*. 2011;20(6):608-18.
10. Egunsola O, Choonara I, Sammons HM. Safety of lamotrigine in paediatrics: a systematic review. *BMJ Open* 2015; 5: e007711.
11. Anderson M, Egunsola O, Cherrill J, Millward C, Fakis A, Choonara I. A prospective study of adverse drug reactions to antiepileptic drugs in children *BMJ Open*. 2015;5(6):e008298.
12. Bansal D, Azad C, Kaur M, Rudroju N, Vepa P, Guglani V. Adverse effects of antiepileptic drugs in North Indian pediatric outpatients. *Clin Neuropharmacol*. 2013;36(4):107-13.
13. Choonara I. Anticonvulsant toxicity in paediatric out-patients. *The Br J Clin Practice*. 1988;42(1):21.
14. Makuch RW. Detecting rare adverse events in postmarketing studies: sample size considerations. *Drug Information Journal*. 2006;40(1):89-98.
15. Anderson M, Choonara I. A systematic review of safety monitoring and drug toxicity in published randomised controlled trials of antiepileptic drugs in children over a 10-year period. *Arch Dis Child*. 2010;95(9):731-8.
16. Egunsola O, Choonara I, Sammons HM. Safety of levetiracetam in paediatrics: a systematic review. *PLoS One* 2016; 11 :e0149686.
17. Dudley RW, Penney SJ, Buckley DJ. First-drug treatment failures in children newly diagnosed with epilepsy. *Pediatr Neurol*. 2009;40(2):71-7.
18. De Silva M, MacArdle B, McGowan M, Hughes E, Stewart J, Reynolds E, et al. Randomised comparative monotherapy trial of phenobarbitone, phenytoin, carbamazepine, or sodium valproate for newly diagnosed childhood epilepsy. *Lancet*. 1996;347(9003):709-13.
19. Guerrini R, Zaccara G, la Marca G, Rosati A. Safety and tolerability of antiepileptic drug treatment in children with epilepsy. *Drug Saf*. 2012;35(7):519-33.
20. Carpay HA, Arts WF, Vermeulen J, Stroink H, Brouwer OF, Boudewyn Peters A, et al. Parent-completed scales for measuring seizure severity and severity of side-effects of antiepileptic drugs in childhood epilepsy: development and psychometric analysis. *Epilepsy Res*. 1996;24(3):173-81.
21. Morita DA, Glauser TA, Modi AC. Development and validation of the pediatric epilepsy side effects questionnaire. *Neurology*. 2012;79(12):1252-8.

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2  
3 22. Marson AG, Appleton R, Baker G, Chadwick D, Doughty J, Eaton B, et al. A Randomised  
4 Controlled Trial Examining the Longer-term Outcomes of Standard Versus New Antiepileptic  
5 Drugs: The SANAD Trial: National Co-ordinating Centre for Health Technology Assessment;  
6 2007.  
7  
8 23. Biton V, Edwards KR, Montouris GD, Sackellares JC, Harden CL, Kamin M. Topiramate titration  
9 and tolerability. *Ann Pharmacother*. 2001;35(2):173-9.  
10  
11 24. Schumock G, Thornton J. Focusing on the preventability of adverse drug reactions. *Hospital*  
12 *Pharmacy*. 1992;27(6):538.  
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