# EpiNet-*First*

**A series of five pragmatic randomised controlled trials comparing the effectiveness of levetiracetam versus lamotrigine, carbamazepine and sodium valproate for untreated epilepsy: the EpiNet-*First* trials**

## Version 2.0 Dated 17th June 2014

## ETHICS REF: 14/NTB/56

**Study Sponsors and Trial Steering Committee:**

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- **Wendyl d'Souza (Australia)**
- **Lynette Sadleir (New Zealand)**
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## Protocol Approval

**Authorised by Chief Investigator:**

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**Signature:** **Date: 09/09/2014**

## General Information

This document describes the EpiNet-*First* trials and provides information about procedures for entering patients into them. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trials. Clinical problems relating to this trial should be referred to the Chief Investigator via the coordinating centre.

This protocol defines the participant characteristics required for study entry and the schedule of treatment and follow-up. Participant recruitment will be undertaken in compliance with this document and applicable regulatory and governance requirements, and waivers to authorise non-compliance are not permitted.

## Statement of Compliance

This study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and subsequent amendments, and will be conducted in compliance with the protocol, Standard Operating Procedures and ICH-GCP guidelines.

## Location of Institutions/Centres

| **EpiNet-*First* Coordinating Centre** |
|---|
| Auckland Hospital<br>2 Park Road<br>Auckland<br>New Zealand |

| Investigator details | | |
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## Independent Advisory Group (IAG)

Independent experts in the field of clinical trials in epilepsy.
This panel will be convened by-

**Associate Professor Ernest Somerville, Nneurologist**,
Chair of the Australian and New Zealand Association of Neurologists'
Director of the Comprehensive Epilepsy Service, Prince of Wales Hospital, Sydney

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## Glossary

| | |
|---|---|
| AE | Adverse Event |
| AED | Anti-epileptic Drugs |
| AR | Adverse Reaction |
| CBZ | Carbamazepine |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CT | Computed Tomography |
| EC | Ethics Committee |
| EEG | Electroencephalogram |
| GP | General Practitioner |
| HR | Hazard Ratio |
| IAG | Independent Advisory Group |
| IEC | Independent Ethical Committee |
| IMP | Investigational Medicinal Product |
| ITT | Intention to Treat |
| LEV | Levetiracetam |
| LTG | Lamotrigine |
| MRI | Magnetic Resonance Imaging |
| PI | Principal Investigator |
| PISC | Patient information Sheet and Consent Form |
| QOL | Quality of Life |
| R&D | Research & evelopment |
| RCTs | Randomised Controlled Trials |
| SAE | Serious Adverse Event |
| SAP | Statistical Analysis Plan |
| SAR | Serious Adverse reaction |
| SVA | Sodium Valproate |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TSC | Trial Steering Committee |
| UAR | Unexpected Adverse Reaction |
| VAS | Visual Analogue Scale |

## 1 PROTOCOL SUMMARY

| | |
|---|---|
| **Title:** | A series of 5 pragmatic randomised controlled trials comparing the effectiveness of levetiracetam, lamotrigine, carbamazepine and sodium valproate for previously untreated epilepsy: EpiNet-*First* trials |
| **Phase:** | IV |
| **Population:** | 1467 patients with focal onset seizures, 1170 patients with generalised onset seizures, and 1840 patients with seizures of uncertain nature.<br><br>**Inclusion Criteria:**<br>□ Aged 5 years or older on date of consent;<br>□ Confident diagnosis of epilepsy (at least 80% certainty)<br>□ Two or more spontaneous seizures that require antiepileptic drug treatment;<br>□ Antiepileptic drug monotherapy considered the most appropriate option;<br>□ Willing to provide consent (patient's parent/legal representative willing to give consent where the patient is aged under 16 years of age)<br><br>**Exclusion Criteria:**<br>□ Provoked seizures (e.g. alcohol, recreational drugs);<br>□ Acute symptomatic seizures (e.g. acute brain haemorrhage or acute brain injury);<br>□ Only absence seizures;<br>□ Psychogenic non-epileptogenic seizures<br>□ Has ever been treated with an antiepileptic for more |
| **Study Centres and Distribution:** | Multinational study. Out-patient epilepsy, general neurology and paediatric (epilepsy and general) clinics |
| **Study Duration:** | Minimum participant duration 2 years<br>Maximum participant duration 5.5 years |
| **Description of Agent/ Intervention:** | All trial medication will be prescribed in a formulation and at a dose deemed suitable by the treating physicians |

**Focal onset seizure participants**
Lamotrigine (LTG), or Carbamazepine (CBZ), or Levetiracetam (LEV)

**Generalised onset seizure participants, if valproate deemed an acceptable AED**

Levetiracetam (LEV), or Valproate (SVA)

**Generalised onset seizure participants, if valproate is NOT deemed an acceptable AED**

Levetiracetam (LEV), or Lamotrigine (LTG)

**Unclassified seizure participants, if valproate deemed an acceptable AED**

Levetiracetam (LEV), or Lamotrigine (LTG), or Valproate (SVA)

**Unclassified seizure participants, if valproate is NOT deemed an acceptable AED**

Levetiracetam (LEV), or Lamotrigine (LTG)

**Primary Objective:** *Time to 12 month remission* - measured using data recorded in participant seizure diaries and seizure data collected at all follow up visits

**Secondary Objectives:**

- *Time to treatment failure**
- *Time to treatment failure due to inadequate seizure control**
- *Time to treatment failure due to unacceptable adverse events**
- *Time to first seizure**
- *Time to 24 month remission**
- *Serious Adverse events (attributed to the trial medication or other anti-epileptic medication)**
- *Proportion of patients who achieve a 12 month remission by 18 months who have not changed to a different AED*
- *Quality Of Life (QOL)*

* Measured using information provided by the patient and clinicians

## 2. BACKGROUND INFORMATION

### 2.1 Introduction

Epilepsy is a common neurological condition, and up to 3% of people will experience seizures at some time in their lives (1). Epilepsy is a complex condition with many different causes, and seizures can take many different forms. It is uniquely stigmatising and has a negative impact on quality of life and employment prospects ( 2 , 3 ) . Antiepileptic drugs (AEDs) are the mainstay of treatment and may have to be taken for life. The goal of treatment is to eliminate seizures at drug doses that do not cause side effects.

Over the past 20 years, a number of new drugs have become available for the treatment of epilepsy. However, there is little data regarding the relative merits of these AEDs in different settings. In particular, the optimal treatment for patients with new-onset epilepsy remains uncertain(4).

**EpiNet Platform**

The EpiNet study group has been established to address areas of uncertainty in the management of patients with epilepsy. We have set up an internet-based platform with the express purpose of running large, simple, low cost, investigator-initiated clinical trials(5, 6). The EpiNet database can be accessed by approved investigators who must log-on to a secure, password-protected website. The database has been designed to prospectively collect data from anywhere in the world on any patient with epilepsy. Information is collected according to a range of axes, including seizure type, electroclinical syndrome, aetiology, investigations and treatment history. Information can be entered directly into the database from the clinic by a neurologist or epileptologist, or a research assistant. This minimizes the need for separate paper forms. All personal data is encrypted before it is transmitted.

The database is extremely comprehensive and versatile, and has been designed to undertake clinical research while simultaneously being used as a clinical tool. It is unique in this regard. The EpiNet platform provides the opportunity to conduct highly focused studies. Algorithms can be written to select patients with particular characteristics, and to randomise them to different treatment groups.

A demonstration of the website is available here: **www.epinet.co.nz**

A pilot study was conducted during 2011 to assess the platform. When the pilot study ended in November 2011, 64 investigators or research assistants from 25 centres in 13 countries had registered 1050 patients (7). Patients with a wide range of epilepsy syndromes and aetiologies were registered. No trials were conducted, but different components of the EpiNet platform were critically assessed.

This international pilot study confirmed that the EpiNet platform is efficient, reliable, secure, and easy to use for doctors from different health systems and cultures. As of January 2014 investigators from the following 20 countries are using the EpiNet database:

New Zealand, Australia, Albania, Belgium, Canada, China, Columbia, Georgia, Great Britain, India, Italy, Korea, Malaysia, Nigeria, Pakistan, Portugal, Serbia, Spain, Sri Lanka, and USA.

In addition to being used to collect data from clinical trials, the EpiNet database can also be used to undertake prospective multicentre cohort studies. Registries can be established for particular patient groups. These registries will be contained within the wider EpiNet database, with specific rules regarding participation and timing of follow-up.

Registries will be established to collect information on patients who are not enrolled in trials, and will therefore provide observational data to supplement the data obtained from the trials.

A First-Seizure Registry and First AED Registry have been established within EpiNet.

### 2.2 Rationale

The EpiNet-*First* trials will be the first clinical trials to be conducted by the EpiNet study group. These trials will focus on patients with newly diagnosed epilepsy for the following reasons:

1) the optimal treatment for patients with new-onset epilepsy remains uncertain;

2) this is a very common clinical problem; it is therefore a good area in which to conduct our first trial, while we grow the collaboration;

3) most patients who develop new onset epilepsy will be eligible for one of these five trials;

4) the EpiNet-*First* trials will be conducted in parallel with the SANAD-ll trials, and will have similar protocols and end-points. SANAD-ll is being conducted in Great Britain with Principal Investigator Professor Tony Marson. We will use the EpiNet platform to run similar trials in countries outside Great Britain, in different populations.

5) Some investigators in Great Britain have informed us that they are not willing to enter women of childbearing age into trials where they may be randomised to receive sodium valproate, since this is clearly teratogenic (8). We therefore intend to run the EpiNet-*First* trial 3 in Great Britain, since patients who are eligible for this trial are unlikely to be enrolled in SANAD-ll

The EpiNet-*First* and SANAD-ll trials will use the same primary endpoints. The EpiNet-*First* protocols are modelled closely on the SANAD-ll protocol, which Professor Marson kindly shared with us, and some sections of the protocols are identical. However, the SANAD-ll trials are being run as non-inferiority trials, whereas the EpiNet-*First* trials are standard superiority trials. Running trials similar to SANAD-ll will also allow investigators to combine datasets for meta-analysis. It will provide a larger dataset to explore whether factors such as epilepsy syndrome or aetiology affect the outcome, or whether different ethnic groups respond differently to particular AEDs. In addition, the SANAD-ll trials will allow us to assess the methodology of the EpiNet-*First* trials. If we get similar results using the EpiNet platform, then it will provide validation of our approach.

EpiNet-*First* will comprise five randomised controlled trials run in parallel. There will be economy of scale given that the protocols are similar, the data structure is almost identical, and the same group of collaborators will be recruiting patients to all five trials. There will be no competition for patients between the five EpiNet-*First* trials as the inclusion criteria are mutually exclusive.

Most patients, aged 5 or older, who present with new onset epilepsy, will be eligible for one or other of these five EpiNet trials, if the AEDs are available at their centres.

As we undertake these trials, we expect to get increasing numbers of epileptologists joining the collaboration. Following the completion of these trials, we anticipate running trials that are more highly focused on specific electroclinical syndromes or aetiologies.

**EpiNet-*First*-Trial 1**

EpiNet-*First* Trial1 will compare lamotrigine, carbamazepine and levetiracetam in patients with untreated focal onset seizures. This trial will recruit patients with focal onset seizures irrespective of aetiology or specific syndrome. Patients are eligible if they have focal seizures with or without impaired consciousness. Patients who have tonic clonic seizures which have a focal onset will be included in this trial. Patients will also be included in this trial if they have generalised seizures which do not have an obvious focal component if they have (had) other seizures that are clearly focal in nature.

**Rationale**

There are numerous AEDs now registered for use in new onset epilepsy. We have chosen to study lamotrigine, carbamazepine and levetiracetam as they are widely used and generally well tolerated.

The SANAD-1 trials compared 5 AEDs in new onset epilepsy(9, 10). The authors concluded that lamotrigine was the drug of choice for patients with focal seizures, since it was more effective than gabapentin, oxcarbazepine and topiramate, and was better tolerated than carbamazepine. However, this conclusion has been challenged, and many experts still regard carbamazepine as the drug of choice for patients with focal seizures(11-13). Many of the current EpiNet investigators have informed us that carbamazepine is still regarded as the drug of first choice for patients with focal seizures in their countries. For these reason, the EpiNet-*First* trial 1 will include arms for both carbamazepine and lamotrigine.

Levetiracetam is a well established antiepileptic drug, and is being increasingly used as a first line treatment for children and adults with focal onset seizures (14, 15). A Cochrane review of 11 short term randomised placebo controlled add-on trials in patients (n=1861) with drug refractory focal onset seizures demonstrated efficacy and tolerability when levetiracetam is used as an add-on treatment (16).

Levetiracetam has also been assessed as monotherapy for patients with focal onset seizures. A short term trial (576 patients) comparing levetiracetam and carbamazepine monotherapy in patients with focal onset seizures found no difference in terms of the

proportion of patients that were seizure free for 6-months (17). The results met an *a-priori* definition of non-inferiority, and the drugs were similar in terms of tolerability. However, the duration of follow-up in this trial is too short to provide information about long-term seizure control, and the trial did not provide quality of life or health economic data. A second industry-sponsored un-blinded trial (the KOMET trial) compared levetiracetam with physicians' choice of carbamazepine (n=992) or valproate (n=696)(18). Although this trial recruited 1688 patients, they were only followed up for a maximum of 12 months, so longer term seizure control could not be assessed. For patients with focal onset seizures levetiracetam and carbamazepine had similar time to treatment failure rates, while time to first seizure suggested an advantage for carbamazepine.

The LaLiMo study was conducted to test the superiority of levetiracetam over lamotrigine in patients with either focal or generalised seizures (19). There was no difference in the primary endpoint - the rate of seizure-free patients at 6 weeks - or the secondary endpoints. However, sodium valproate was not included in this trial, and 40% of the patients had protocol violations. Fewer than 10% of the patients included were children, and none were aged less than 12 years. Twenty per cent of the patients had experienced only a single seizure, and these patients had a lower relapse rate than those patients who had had 2 or more seizures. In addition, this study did not assess sustained seizure-freedom.

Zonisamide is included in Arm A of the SANAD-11 trial (i.e. the SANAD-11 trial for patients with focal seizures.) Zonisamide is not included in EpiNet-*First* Trial 1 since it is not marketed in many of the countries in which the EpiNet-*First* trials are being undertaken.

**Carbamazepine and Severe Skin Reactions**

All anti-epileptic drugs can cause serious side effects and the use of both carbamazepine and lamotrigine can be associated with a hypersensitivity reaction which may involve a severe skin disorder (Stevens-Johnson Syndrome (SJS) or Toxic Epidermal Necrolysis (TNS). These reactions are estimated to occur in 1 to 6 per 10,000 new users of carbamazepine in countries with mainly Caucasian populations (20, 21); however, the absolute risk appears to be higher in some Asian populations. It has recently been discovered that patients who have the HLA-B*1502 haplotype are at relatively high risk of SJS or TNS; this haplotype is more common in patients with particular Asian ethnicities(22). Avoiding the use of carbamazepine in patients from Taiwan substantially reduced the incidence of SJS/TENS(23). In December 2007, the American FDA advised that screening for HLA-B*1502 should be performed for most patients of Asian ancestry before they are prescribed carbamazepine(24).

The FDA made the following points:

- 10-15% or more of patients may carry the allele in parts of China, Thailand, Malaysia, Indonesia, the Philippines, and Taiwan.

- South Asians, including Indians, appear to have intermediate prevalence of HLA-B*1502, averaging 2 to 4%, but higher in some groups.
- HLA-B*1502 appears to be present at a low frequency, <1%, in Japan and Korea.

However, the website also states that that the prevalence of HLA-B*1502 has not been studied in many regions of Asia, and these figures must therefore be considered no more than a rough guide in deciding which patients to screen.

The data sheet for Tegretol (trade name for carbamazepine) presents similar incidence figures and also states:

> The frequency of the HLA-B*1502 allele is negligible in persons of European descent, several African populations, indigenous peoples of the Americas, Hispanic populations sampled and in Japanese (< 1%)

It is not known whether the presence of the HLA-B*1502 allele increases the risk of hypersensitivity reactions to lamotrigine.

It has also been reported that Caucasian patients who have the HLA-A*3101 haplotype are at increased risk of skin rash(25). The clinical significance of this is less clear, and at the present time there are no requirements for patients to be tested for this haplotype. In particular, the American FDA has not stipulated that testing for this haplotype should be performed. The benefit of testing is in part determined by the frequency of the allele in a particular population. It has been estimated that testing for this haplotype in all European patients, and avoiding the use of carbamazepine in patients with the A*3101 allele would prevent 1 in 82 cases of hypersensitivity to carbamazepine.

The data sheet for Tegretol (trade name for carbamazepine) states:

> Testing for the presence of HLA-A*3101 allele should be considered in patients with ancestry in genetically at-risk populations (for example, patients of the Japanese and Caucasian populations, patients who belong to the indigenous populations of the Americas, Hispanic populations, people of southern India, and people of Arabic descent), prior to initiating treatment with Tegretol ... The use of Tegretol should be avoided in patients who are found to be positive for HLA-A*3101, unless the benefits clearly outweigh the risks.

An informal survey of EpiNet investigators who have expressed an interest in participating in the EpiNet-*First* Trials has indicated that none of the investigators currently test for the HLA-A*3101 haplotype before they prescribe carbamazepine. It is clear, therefore that testing for this allele is not currently the standard of care.

It is not known whether the presence of either the HLA-B*1502 allele or the HLA-A*3101 allele increases the risk of hypersensitivity reactions to lamotrigine.

Investigators will need to confirm that any (each) of the three AEDs (levetiracetam, lamotrigine and carbamazepine) is suitable for each particular patient before the patient can be recruited into the EpiNet-*First* Trial1. Each investigator will determine whether HLA testing should be performed, according to their current practice.

**EpiNet-*First* Trial-2**

The EpiNet-*First* Trial 2 will compare levetiracetam and valproate in patients with generalised onset seizures, provided the patient does not have absence seizures alone. Patients need to be willing to take sodium valproate, and investigators need to be prepared for patients to be randomised to sodium valproate.

**Rationale**

Valproate is widely regarded as drug of choice for patients with generalised onset seizures, but without evidence from randomised controlled trials to support this recommendation. A number of Cochrane reviews compared valproate with other antiepileptic drugs including carbamazepine (26), and phenytoin (27), but due to problems with power and epilepsy classification, these have not demonstrated an advantage for valproate. In Arm B of SANAD-I (9), valproate was compared with the newer drugs lamotrigine and topiramate. Valproate was identified as being significantly more effective than lamotrigine and significantly better tolerated than topiramate.

However valproate is associated with a higher rate of teratogenicity than other AEDs (major malformation rate ~8%) (8, 28). There is also evidence that valproate can affect the intellectual development of children exposed in utero with up to one third of children having a significant reduction in their IQ (29, 30). We will therefore advise women of childbearing age not to participate in EpiNet-*First* Trial 2 if there is any prospect that they might become pregnant. Instead, we will encourage these women to participate in EpiNet-*First* Trial-3 .

A number of studies have demonstrated efficacy of levetiracetam as an add-on treatment for patients with refractory generalised epilepsy. A randomised placebo controlled trial of add-on levetiracetam in patients (n=122) with juvenile myoclonic epilepsy found that levetiracetam significantly reduced myoclonic seizures, which was the primary outcome in the trial (31). A second randomised placebo controlled trial assessed add-on levetiracetam in adults and children (229 participants) with drug refractory generalised epilepsy. This trial found a significant reduction in the frequency of generalised tonic clonic seizures with levetiracetam compared to placebo (32). Based largely on this evidence, levetiracetam was subsequently granted a license as add-on treatment for such patients. In the un-blinded KOMET trial, physicians' choice of valproate was compared with levetiracetam (n=696). As indicated above, this trial was too short to assess longer term outcomes, but time to treatment failure rates were similar for valproate and levetiracetam, and time to first seizure had a trend in favour of valproate(18).

This body of evidence provides data to support levetiracetam as a potential first-line treatment for patients with generalised onset seizures. It is important that its long-term effectiveness is assessed, particularly to inform decisions made by women of child-bearing potential.

Patients will not be included in EpiNet-*First* Trial 2 if they only experience absence

seizures. Patients who have experienced one or more absence seizures must also have had at least one other form of generalised seizure to be enrolled in EpiNet-*First* Trial 2. This is because ethosuxamide has been shown to be as effective as valproate in controlling absence seizures, and more effective than lamotrigine (33, 34). Ethosuxamide is not generally regarded as a first choice treatment for tonic-clonic seizures. The evidence regarding the effectiveness of levetircaetam in treating absence seizures is conflicting (35, 36), and we are not studying the role of levetircaetam in treating absence seizures when they are the only seizure type. We are including patients with myoclonic seizures in EpiNet-*First* Trial 2 even if they have not had any tonic clonic seizures. All seizure types will be considered as end-points.

Patients will be further classified by syndrome where and when such a syndromic diagnosis can be made; however, patients will not be stratified according to the epilepsy syndrome. The influence of seizure type and syndrome upon treatment outcome can then be investigated in prognostic models.

EpiNet-*First* Trial 2 differs from SANAD-11 because we are not including patients with seizures that are difficult to classify in this particular trial. We think this group is likely to include patients with focal seizures, and these patients may contaminate the interpretation of treatment of generalised seizures. We are enrolling these patients in separate studies (EpiNet-*First* Trials 4 and 5)

**EpiNet-*First* Trial 3**

EpiNet-*First* Trial-3 will compare levetiracetam and lamotrigine in patients with generalised onset seizures who are not prepared to take valproate. The entry criteria will be the same as for EpiNet-*First* Trial-2 except that patients are not prepared to take valproate, or their doctors are not prepared to randomise them to this drug.

**Rationale**

Prior to the publication of SANAD-I, lamotrigine was considered a first line alternative for patients with generalised onset seizures, but data from SANAD-I show that it is significantly less effective than valproate in this patient group(9). However, lamotrigine is considerably less teratogenic than valproate and is generally regarded as a drug of choice for women with epilepsy who wish to become pregnant(8).

SANAD-I demonstrated that sodium valproate is more effective than lamotrigine in patients with generalized seizures, but there remains uncertainty regarding the relative merits of lamotrigine and levetiracetam in patients for whom sodium valproate is not suitable. Patients with generalized-onset seizures who are eligible for an EpiNet-*First* study will therefore be stratified. If both levetiracetam and sodium valproate would be acceptable AEDs, then patients will be enrolled in EpiNet-*First* Trial 2 and be randomised to one of these drugs. However, if sodium valproate is deemed unacceptable, patients will be entered into EpiNet-*First* Trial-3 and randomised to either lamotrigine or levetiracetam.

Entry criteria for EpiNet-*First* Trial-3 will be exactly the same as for EpiNet-*First* Trial 2, apart from the appropriateness of valproate

**EpiNet-*First* Trial 4**

The EpiNet-*First* Trial 4 will compare levetiracetam, lamotrigine and valproate in patients with seizures that cannot be classified. If patients are not willing to take sodium valproate, they will be randomised to either levetiracetam or lamotrigine (EpiNet-*First* Trial 5.)

**Rationale**

The SANAD-1 Arm B combined patients who had generalised seizures with those whose seizures could not be classified. We are concerned that combining these groups mixes patients whose seizures may respond to different drugs. In particular, we are concerned that some patients whose seizures are unclassified are likely to have focal seizures, and these patients may respond to different AEDs from patients with generalised seizures. We do not think that SANAD-1 B has informed physicians what the optimal treatment is for patients where the doctor is genuinely unsure of the nature of the seizure type. We are not convinced that SANAD-1 B has shown that valproate is superior to lamotrigine in this patient group(9). We are therefore comparing levetiracetam, lamotrigine and valproate in this trial.

We think it is important to include this arm of the trial because we want to allow investigators the option of including as many patients with newly diagnosed epilepsy who are being started on an AED as possible. We do not want patients with unclassified seizure types being squeezed into the group with generalised seizures, or the group with definite focal seizures.

**EpiNet-*First* Trial 5**

**Rationale**

As discussed above, valproate may not be deemed appropriate for some patients - particularly women of child-bearing age. Patients with unclassified seizures who are eligible for the EpiNet-*First* study will therefore be stratified. The investigator will be asked whether all of levetiracetam, lamotrigine and sodium valproate would be acceptable AEDs, and if so, the patient will be randomised to one of these three AEDs. If sodium valproate is deemed unacceptable, patients will be entered into EpiNet-*First* Trial 5 and randomised to either lamotrigine or levetiracetam.

Entry criteria for EpiNet-*First* Trial 5 will be exactly the same as for EpiNet-*First* Trial 4, apart from the appropriateness of valproate

### 2.3 Objectives

**EpiNet-*First*-Trial 1** - To determine whether levetiracetam is more effective than either lamotrigine or carbamazepine when used as monotherapy in patients with untreated focal-onset seizures.

**EpiNet-*First* Trial 2** - To determine whether levetiracetam is more effective than valproate in patients with untreated generalised-onset seizures. (Patients with absence seizures alone are not included.)

**EpiNet-*First*-Trial 3 –** To determine whether levetiracetam is more effective than lamotrigine in patients with untreated generalised-onset seizures for whom valproate is not suitable. (Patients with absence seizures alone are not included.)

**EpiNet-*First*-Trial 4** - To determine whether levetiracetam is more effective than lamotrigine or valproate in patients with untreated seizures of uncertain nature.

**EpiNet-*First*-Trial 5** - To determine whether levetiracetam is more effective than lamotrigine in patients with untreated seizures of uncertain nature, for whom valproate is not suitable.

A full list of outcome measures is presented in section 4.

### 2.4 Potential Risks and Benefits

The recruiting clinician will discuss the potential risks and benefits with patients prior to trial entry and they will be outlined in the patient information sheet.

#### 2.4.1 Known Potential Risks

None of the AEDs being studied in the EpiNet-*First* group of trials are experimental drugs. All of them have been registered and are in widespread use in many countries over a number of years. The risk profiles are well known. People who have the HLA-B*1502 haplotype have a significant risk if they are given carbamazepine; otherwise, there is a small risk of an idiosyncratic drug reaction for any of these AEDs. The main risk of EpiNet-*First* is that patients may be allocated to a treatment that on final analysis is found to be less effective than another treatment, or have a higher adverse event rate. However, there is currently clinical equipoise among the treatments being tested. Participants can be switched from their allocated treatment if a decision is made by the prescribing physician and patient that seizure control is inadequate or adverse events are unacceptable.

#### 2.4.2 Known Potential Benefits

Patients recruited into the EpiNet-*First* trials will receive standard care during the conduct of the trials. The main potential benefit is that patients might receive treatment with a drug which is either more effective and/or better tolerated than the alternative treatment.

Their participation will help determine which of the AEDs being studied is the more

effective agent. Patients may also receive closer medical attention because they are in the trial than may have occurred in other circumstances.

## 3. SELECTION OF CENTRES / CLINICIANS

The EpiNet-*First* trials will take place in out-patient epilepsy clinics, general neurology clinics and paediatric (epilepsy and general) clinics in any centre in the world where there are approved EpiNet investigators who have received the appropriate approvals from their ethics committees and local research body. The study will be coordinated through the EpiNet-*First* coordinating centre which will be based in Auckland, New Zealand.

A formal validation test of the EpiNet study group is currently underway. Only investigators who provide acceptable results in the validation study will be accredited to participate in the EpiNet-*First* trials. Accreditation records will be kept at the coordinating centre in Auckland, New Zealand and kept in the study file.

Study centres will be initiated once ethics approval and any local R&D/locality approvals have been obtained, and study-specific conditions (e.g. training and accreditation requirements) have been met, and all necessary documents have been returned to the coordinating centre (which can be done electronically as a PDF file).

This protocol covers all five of the EpiNet-*First* trials, and these trials will be run simultaneously. However, particular centres and investigators do not need to participate in all 5 trials. For various reasons (such as a high prevalence of HLA B*1502 haplotype), some centres may decide not to participate in a particular trial. Individual investigators may therefore participate in anywhere between one and five of the EpiNet-*First* trials.

### 3.1 Centre / Clinician Inclusion Criteria

a. Experienced in treating pilepsy.
b. Ethical and Local organisational approvals.
c. Each of the AEDs being studied in a particular trial is registered in the country.
d. Accreditation of investigator by successful participation in the EpiNet Validation study.
e. Receipt of evidence of completion of (b) and (d) by the coordinating centre.

### 3.2 Centre / Clinician Exclusion Criteria

a. Not meeting all the inclusion criteria listed above

## 4. TRIAL DESIGN

### 4.1 Primary Endpoint

The primary endpoint for each of the 5 EpiNet-*First* trials is time to 12 month remission from seizures; the time (T0) will start from the date of randomisation, even if the patient commences the AED on another day. (The time will be taken from the date of randomisation, rather than the date of the last seizure which preceded randomisation.)

### 4.2 Secondary Endpoint(s)

a. Time to treatment failure, due to either inadequate seizure control, or due to unacceptable adverse events. Treatment failure due to inadequate seizure control will have occurred when the clinician and/or patient decide that treatment withdrawal, or the addition of a second antiepileptic drug is required due to the occurrence of a seizure on the maximum recommended dose of randomised drug, or the maximum tolerated dose of the drug; treatment failure due to unacceptable adverse events will have occurred when the patient experiences adverse events attributed to the drug necessitating its withdrawal.

b. Time to treatment failure due to inadequate seizure control.

c. Time to treatment failure due to unacceptable adverse events.

d. Time to first seizure;

e. Time to 24 month remission;

f. Serious Adverse events attributed to the trial medication or other anti-epileptic medication;

g. Proportion of patients who achieve a 12 month remission by 18 months who have not changed to a different AED;

h. Quality of life (QOL) (assessed using QOLIE31)(37)

## 5. STUDY POPULATION

The EpiNet-First trials will be conducted in people with new onset epilepsy, who have never been treated with anti-epileptic drugs for more than one week. Separate trials will be run for patients with focal seizures, generalised seizures, and seizures whose nature is uncertain. Altogether, 1467 patients with focal onset seizures, 1170 patients with generalised onset seizures, and 1840 patients with seizures of uncertain nature will be recruited.

### 5.1 Inclusion Criteria

Patients with the following characteristics will be eligible for inclusion in the trial:

a) Aged 5 years or older on date of consent;

b) The investigator is confident that the patient has epilepsy (at least an 80% level of confidence);

c) Two or more spontaneous seizures that require antiepileptic drug treatment (focal or generalized, provided all seizures have not been absence seizures);

d) Antiepileptic drug monotherapy considered the most appropriate option, and each of the AEDs for the particular trial considered by the investigator to be appropriate;

e) Willing to provide consent. For patients younger than the age of consent (usually 16 years), patient's parent/legal representative willing to give consent, and the patient willing to give assent (details depending on country-specific requirements)

### 5.2 Exclusion Criteria

Patients with the following characteristics will be excluded from the trial:

a) Seizures provoked by alcohol or recreational drugs;

b) Acute symptomatic seizures (e.g. acute brain haemorrhage or brain injury);

c) Only absence seizures;

d) Is thought to have psychogenic non-epileptogenic seizures

e) Has ever been treated with an antiepileptic for more than one week;

f) Known progressive neurological disease (e.g. known brain tumour).

### 5.3 Cessation/Change of AED Treatment, Patient Transfer and Withdrawal

In consenting to the trial, patients are consenting to trial treatment, follow-up and data collection. If withdrawal of the randomly allocated treatment occurs, patients should still be followed up to allow a thorough assessment of the treatment policies, as patients may still achieve the primary outcome (12 month remission) following withdrawal of randomised treatment.

### 5.3.1 Cessation/Change of AED Treatment

If withdrawal of the randomly allocated treatment occurs (either due adverse events or insufficient efficacy), or additional AEDs are added to the randomly allocated treatment patients should still be followed up to allow a thorough assessment of the treatment policies, as patients may still achieve the primary outcome (12 month remission) following withdrawal of randomised treatment.

### 5.3.2 Patient Transfers

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating trial centre and for this trial centre to take over responsibility for the patient.

A copy of the participant's EpiNet record will be attached to the cohort of the investigator at the new site. The patient (or parent / legal representative) will have to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the original centre.

### 5.3.3 Withdrawal from Trial Completely

Patients (or patients parent / legal representative where the patient is aged under 16 years of age) are free to withdraw consent at any time without providing a reason. Patients who wish to withdraw consent to participate in the trial will have anonymised data collected up to the point of that withdrawal of consent included in the analyses. The patient will not contribute further data to the study. A consent withdrawal form should be completed and the reason for trial withdrawal should be recorded in the EpiNet record. Data up to the time of withdrawal will be included in the analyses unless the patient explicitly states that this is not their wish.

## 6. ENROLMENT AND RANDOMISATION

### 6.1 Screening

All patients aged 5 years and over, who have had two or more spontaneous seizures that require antiepileptic drug treatment, and have not been treated with any antiepileptic drug for more than one week will be screened at the study centres to identify potentially eligible participants for the study. These patients will all have records created in the EpiNet database. Investigators will be encouraged to record data prospectively in the First-AED registry within EpiNet, even if the patients are not included in any of the EpiNet-*First* trials. Reasons for non-participation will be recorded. Reasons for declining to participate will be asked routinely but it will be made clear that patients, parents or carers do not have to provide a reason unless happy to do so.

Potentially eligible patients (i.e. those that meet the eligibility criteria listed in section 5) or their parent / legally acceptable representative where appropriate, will be invited to participate in the study and provided with a patient information sheet and consent form. The patient (or parent / legally acceptable representative where appropriate) will be allowed sufficient time to discuss the trial and decide whether to consent to trial entry (see section 11.3 for consent procedures). Children who are old enough to read and understand the concepts relating to a clinical trial will be offered a separate assent form.

### 6.2 Baseline

Once consent has been obtained from the patient (or parent / legal representative where applicable, and assent by the child where appropriate and applicable) the delegated member of the research team e.g. research nurse/consultant should record the required baseline data (which will include seizure history, history of neurological insult, febrile seizures, family history of epilepsy, EEG and imaging (CT or MRI) results) into the EpiNet record. If further investigations (EEG or imaging) are requested at this visit, data on results will be collected when available, but randomisation need not be delayed. If the patient is confirmed eligible then the research team should proceed to randomise the patient.

### 6.3 Randomisation

Patients **should not** be randomised until:

a) Consent has been obtained from the patient (parent / legal representative where the patient is under 16 years of age)

b) The minimum baseline data has been recorded into the EpiNet record;

c) Eligibility criteria have been fulfilled.

The trial in which the patient will be enrolled will be determined by the seizure type and the willingness of the patient to take valproate. Investigators will be guided through this process by algorithms within the EpiNet database. Investigators will be asked what type of seizures the patient has, and whether the patient would be willing to take valproate. Patients will then be randomised to one of the following treatments:

For each of the trials, randomisation will be by block randomisation with variable block size to minimize any potential for predicting allocation. Randomisation will be stratified by country, age (below 18 vs 18 or older) and sex.

Patients who have focal seizures will be entered into the **EpiNet-*First* Trial 1,** and randomised to receive either levetiracetam or lamotrigine or carbamazepine (in a 1:1:1 ratio).

Patients who have generalised seizures (excluding patients who have a focal onset to their seizures, or who have absence seizures alone) who are willing to take valproate will be entered into the **EpiNet-*First* Trial 2** and randomised to receive either levetiracetam or valproate (in a 1:1 ratio),

Patients who have generalised seizures (excluding patients who have a focal onset to their seizures, or who have absence seizures alone) who are NOT willing to take valproate will be entered into the **EpiNet-*First* Trial 3** and randomised to receive either levetiracetam or lamotrigine (in a 1:1 ratio)

Patients who have seizures of uncertain nature who are willing to take valproate will be entered into the **EpiNet-*First* Trial 4** and randomised to receive either levetiracetam or lamotrigine or valproate (in a 1:1:1 ratio).

Patients who have seizures of uncertain nature who are NOT willing to take valproate will be entered into the **EpiNet-*First* Trial 5** and randomised to receive either levetiracetam or lamotrigine (in a 1:1 ratio).

Participants will be randomised from within the EpiNet database, using a secure (24-hour) web based randomisation programme. Personal login username and password will be required to access the EpiNet database and the web-based randomisation system. When eligibility has been confirmed the participant will be randomised. Treatment allocation will be displayed to the authorised randomiser on a secure webpage within the EpiNet record, and an automated email confirmation will be sent to the authorised EpiNet investigator, PI and the trial coordinator.

*If there are any problems with the randomisation systems, please contact the EpiNet-First coordination service via e-mail: helpdesk@enigma.co.nz*

## 7. TRIAL TREATMENTS

### 7.1 Introduction

EpiNet-*First* comprises five randomised controlled trials run in parallel. Depending on the specific trial, patients will be randomised to receive either levetiracetam, lamotrigine, carbamazepine or valproate.

Randomised treatment should begin within 7 days of randomisation. The research team should ensure that any delay before starting the trial treatment does not impact on the well-being of the participant. Assessments that should be carried out prior to the start of the randomised treatment are detailed in sections 6 and 8.

All treatments will be prescribed and issued as per routine practice. Generic versions of AEDs can be prescribed, if these are routinely used in a particular centre. Specific details regarding which version of an AED is used will be recorded.

If a patient has already been commenced on an AED, he can only be recruited for any of the EpiNet First trials if:

- he/she has taken the AED for 7 days or less;
- he/she agrees to be randomised to one of the treatment arms for the trial for which the patient is eligible. (In some circumstances, it may be possible for the patient to be randomised to the drug which he/she is already taking.)
- the investigator considers that it is appropriate to include the patient in the trial.

In these circumstances, if a patient is randomised to another AED, the original AED should be withdrawn according to the investigator's standard clinical practice. In most circumstances, since the patient will have used the drug for only a few days, it will be appropriate to discontinue the AED immediately. The new AED (to which the patient has been randomised) will be introduced according to routine clinical practice. If appropriate, the two drugs can be overlapped for a brief period. Full details including the dates on which the original AED was commenced and discontinued, and the dose used, should be recorded in the EpiNet record.

If a patient is randomised to the same AED that he / she was already taking, the drug should simply be continued and/or increased according to routine practice. The date on which the patient started the drug should be recorded in the EpiNet record, even if that date is earlier than the date of randomisation. Outcome data will be calculated from the date of randomisation.

Patients will be recruited over a 3.5 year period and follow up will continue for a further two years. Thus the maximum time that a patient will participate in any of the trials is 5.5 years.

### 7.2 Formulation, Packaging, Labelling, Storage and Stability

EpiNet-*First* comprise pragmatic trials that use authorized drugs within the terms of marketing authorization. The EpiNet-*First* trials are therefore categorized as ***Type A*** *with* ***"no higher than the risk of standard medical care"*** (see section 12.1). All treatments will be taken as tablets and capsules already licensed to be used in the participant's country. There will be no modifications made to the products or their outer packaging, and therefore a pharmacy label is sufficient when the treatment is dispensed against a prescription.

The products can be dispensed by hospital and community pharmacies as they would be normally in clinical practice. It is the responsibility of the investigator to ensure that the GP is prepared to prescribe the remainder of any trial treatment not dispensed by the hospital pharmacy.

All treatments should be stored as per normal clinical practice. Please refer to the reference Medicine Data Sheets for your country; this should be kept within the site study file.

### 7.3 Preparation, Dosage and Administration of Study Treatments

All patients should be titrated to an initial maintenance dose, with dose adjustments made at subsequent appointments according to clinical response and adverse effects. Guidelines for titration and initial maintenance dose are outlined below. However, clinicians will be able to alter this to choose the titration rate and initial maintenance they think most appropriate for individual patients according to their usual practice. Doses outside the recommended range will be highlighted in EpiNet to check that the investigator has not made an error.

**Recommended Titration and Initial Maintenance Doses for AEDs prescribed**

**Levetiracetam**

**Age > 12 years: Titration and Initial Maintenance Dose**

250mg once per day for 2 weeks
250mg twice per day for 2 weeks
250mg morning and 500mg evening for 2 weeks
500mg twice per day - *initial target maintenance dose*

**Children aged 5-12: Titration and Initial Maintenance Dose**

10 mg/kg/day as a twice daily regimen for 2 weeks
20 mg/kg/day as a twice daily regimen for 2 weeks
30 mg/kg/day as a twice daily regimen for 2 weeks
40 mg/kg/day as a twice daily regimen – *initial target maintenance dose*

**Lamotrigine**

**Age > 12 years: Titration and Initial Maintenance Dose**

25mg once per day for 2 weeks
25mg twice per day for 2 weeks
50mg twice per day for 2 weeks
50mg morning and 100mg at night - *initial target maintenance dose*

**Children aged 5-12: Titration and Initial Maintenance Dose**

0.5 mg/kg/ day as a once a day dose for 2 weeks
1.0 mg/kg/day as a twice daily regimen for 2 weeks
0.5 mg/kg am and 1.0 mg/kg pm for 2 weeks
1.0 mg/kg am and 1.0 mg/kg pm for 2 weeks
1.5 mg/kg am and 1.5 mg/kg pm – *initial target maintenance dose*

**Carbamazepine**

**Age > 12 years: Titration and Initial Maintenance Dose**

100 mg once per day for 2 week
100 mg twice per day for 2 week
100 mg mane, 200mg nocte for 2 weeks
200 mg bd thereafter – *initial target maintenance dose*

**Children aged 5-12: Titration and Initial Maintenance Dose**

5 mg/kg/day for 2 week,
10 mg/kg//day for 2 week,
20 mg/kg/day thereafter – *initial target maintenance dose*

**Valproate**
**Age > 12 years: Titration and Initial Maintenance Dose**

500mg once per day for 2 weeks
500mg twice per day - *Initial maintenance dose*

**Children aged 5-12: Titration and Initial Maintenance Dose**

10 mg/kg/day as a twice daily regimen for 2 weeks
15 mg/kg/day as a twice daily regimen for 2 weeks
25 mg/kg/day as a twice daily regimen – *initial target maintenance dose*

### 7.4 Unblinding

EpiNet-*First* trials are open-label trials and therefore unblinding is not required.

### 7.5 Accountability and Assessment of Compliance with Study Treatments

EpiNet-*First* trials are pragmatic rather than exploratory trials and the intention is to measure outcomes associated with treatment policies which reflect real life clinical practice. There are no formal accountability measures required for the trials, as treatments will be prescribed according to the local medical practices and dispensed by hospital and community pharmacies as would be normal in clinical practice.

It is accepted that, for a variety of reasons including perceived or actual efficacy and tolerability, not all patients will take their medicines as prescribed. Patients will be encouraged to take their medication as prescribed, and they will be asked about adherence, but no formal measurements of plasma drug levels are planned. The primary analyses will not be adjusted for actual or estimated adherence.

### 7.6 Concomitant Medications / Treatments

EpiNet-*First* trials are unblinded and therefore decisions about concomitant medications / treatments will depend on the local medical plan and clinical management.

### 7.7 Dose Modifications

The aim of treatment will be to control seizures with a minimum effective dose of drug. This will necessitate dosage modification if further seizures or adverse events occur, as is usual clinical practice. The decision to discontinue allocated trial treatment is at the discretion of the treating physician and patient. Treatment may be discontinued at any point during the trial period for reasons such as inadequate seizure control, unacceptable adverse events, or any change in the participant's condition that the physician believes warrants a change in medication. Any changes in medication must be documented in the EpiNet record along with the reason for those changes. If a participant's treatment stops prematurely, the reason for discontinuation should be recorded in the EpiNet record, and the patient should still be encouraged to attend follow up visits for the remainder of the study.

At the end of trial participation the participants may continue their treatment as per local policy.

### 7.8 Co-enrolment Guidelines

To avoid potentially confounding issues, ideally patients should not be recruited into other trials. Where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the EpiNet-*First* trial this must first be discussed

with the coordinating centre who will contact the Chief Investigator (Dr Peter Bergin).

## 8 ASSESSMENTS AND PROCEDURES

Data will be entered directly into the EpiNet records, on-line. There are no separate Case Record Forms (CRFs) for data entry.

Participating centres will be expected to each maintain a file of essential trial documentation (Site File), and keep copies of all paper documents, including signed consent forms and seizure diaries for the trials.

Once the baseline information has been entered into the EpiNet record, the EpiNet-*First* algorithms will determine whether the patient is eligible for any of the EpiNet-*First* trials; if so, the patient will be randomised and followed-up in the trial. Each patient screened will be allocated a unique screening number, and each patient randomised will be assigned a unique subject number. Subject numbers will be trial-specific. For screening and randomisation procedures refer to section 6. For details of procedures associated with trial treatments refer to section 7.

Participant details including name, initials, date of birth and subject number will be reported on the consent form.

### 8.1 Schedule for Follow-up

The expected duration of each participant is between a minimum of 2 years and a maximum of 5.5 years. All participants will be followed up whether they are still taking their allocated treatment or not. Where patients default from clinic follow-up, additional information will be sought from GPs, and where necessary patients will be contacted directly for follow up information.

Patients will be followed up at 3 and 6 months post randomisation, and at 6 month intervals thereafter, until the trial ends or they have been seizure-free for 2 years. Patients will be seen at other times as clinically indicated. The delegated member of the research team should update the EpiNet record whenever a patient is seen.

Where treatment is stopped the participant will be asked to continue with trial follow-up and attend the follow-up visits. If a participant does not wish to continue in the trial, a Consent Withdrawal form will be completed and EpiNet will be up-dated to capture the date and reason for trial withdrawal as detailed in section 5.3.2.

**Table 1: Trial Assessments**

Follow Up Schedule

| Procedures | Baseline[1] | T0+3 months | T0+6 months | T0+12 months + 6 |
|---|---|---|---|---|
| Signed Consent Form | X | | | |
| Baseline data entered into EpiNet record | X | | | |
| Assessment of Eligibility Criteria | X | | | |
| Review of Medical History including:<br>• Seizure history<br>• Neurological insult<br>• Febrile seizures<br>• Family history of epilepsy<br>• EEG results (if possible) | X | | | |
| Further investigation (EEG / CT/ MRI) | (X) | | | |
| Allocation of Study Treatment | X | | | |
| Review of seizure occurrence & hospital admissions | | X | X | X |
| Review of Anti Epileptic Drug Use (Study Treatment & Concomitant): | | X | X | X |
| Assessment of QOL | X | X | X | X |

(X) – As indicated/appropriate.

1 At baseline, all procedures should be done before study intervention.

### 8.2 Procedures for assessing Efficacy

Efficacy of the trial treatments will be measured through the period of the trial using a number of measures.

#### 8.2.1 Seizure Diaries

Data on seizures recorded in patient seizure diaries, including number, type and date, will be captured at follow up visits and transcribed to the EpiNet record.

#### 8.2.2 Quality of Life Scores

The VAS score of the QOLIE31 (Section 8.4) obtained throughout the trial can be used as a subjective measure of efficacy.

### 8.3 Procedures for Assessing Safety

Only Serious Adverse Events will be reported, using a special Serious Adverse Event form in the EpiNet record. As well as reporting these to the Trial Coordinating centre, serious adverse reactions should also be reported to the relevant authorities in the Investigator's own country.

### 8.4 Quality of Life Assessments

Adult patients (18 years and over) will be asked to complete the Visual Analogue Scale from the QOLIE 31 questionnaire(37). Participants aged 16-17 will complete the QOLIE-AD-48 for adolescents. Parental proxy reports of (health-related) quality of life will be used for those under age 16 (38).

The Visual Analogue Scale (VAS) to be completed at baseline will be provided to the participant and / or parent as applicable on the day of randomisation by a member of the research team. The VAS should also be completed at each study visit where possible.

### 8.5 Loss to Follow-up

If any of the trial patients are lost to follow up, contact will initially be attempted through the research team at each centre. If the lead investigator at the trial centre is not the patient's usual clinician responsible for their epilepsy care, then follow-up will also be attempted through this latter clinician. Where these attempts are unsuccessful, the patient's GP will be asked to contact the patient and provide follow-up information to the recruiting centre. Wherever possible, information on the reason for loss to follow-up will be recorded.

### 8.6 Trial Closure

The end of the trial is defined to be the date on which data for all participants is

frozen and data entry privileges are withdrawn from the trial database. However, the trial may be closed prematurely by the Trial Steering Committee (TSC), on the recommendation of the Independent Advisory Group (IAG).

## 9. STATISTICAL CONSIDERATIONS

### 9.1 Introduction

Statistical analyses will be performed on each individual trial separately, using SAS version 9.3 (SAS Institute Inc. Cary NC). Trial data will be collected using the EpiNet web-based database, and extracted into SAS for data quality checks and final statistical analysis when all patients have a minimum two year follow-up data at the end of the trial.

All primary analyses of time to 12 month remission from seizures will be on an intention to treat (ITT) basis including all randomised patients regardless of whether they actually satisfied the entry criteria, the treatment actually received, and subsequent withdrawal or deviation from the protocol. Secondary per protocol (PP) analyses will also be undertaken to assess the robustness of ITT analyses. This analysis will include all randomised patients who have taken the prescribed study drug and who do not have major protocol violations. All statistical tests will be two-sided and a 5% significance level maintained throughout the analyses. Confidence intervals for all point estimates will be two-sided 95% intervals.

### 9.2 Sample Size

For each trial, the proposed sample size will provide 90% power at 5% significance level (two-sided) to identify a 10% or greater difference in 12 month disease-free survival at 2 years between the groups, allowing for 10% loss to follow up. This difference is considered to be the minimum clinically important difference. The estimated survival rates were based on 12 month disease free survival at 24 months in the SANAD-1 trials. 67% of patients randomised to lamotrigine and 70% randomised to carbamazepine in SANAD1A achieved the endpoint of 12 months remission of seizures; 78% of those randomised to sodium valproate and 73% of those randomised to lamotrigine in SANAD1B achieved this endpoint (9, 10)

- EpiNet-*First* Trial 1 Patients with focal seizures will be randomised to receive either levetiracetam or lamotrigine or carbamazepine. (489 patients will be required in each arm; 1467 in total.)
- EpiNet-*First* Trial 2 Patients with generalised seizures (except those with absence seizures only) will be randomised to receive either sodium valproate or levetiracetam. (253 in each arm; 506 in total.)
- EpiNet-*First* Trial 3 Patients with generalised seizures (except those with absence seizures only), and sodium valproate is deemed unsuitable (e.g. in women of childbearing age), then patients will be randomised to either lamotrigine or levetiracetam. (332 in each arm; 664 in total.)

- EpiNet-*First* Trial 4 Patients with seizures of unknown nature will be randomised to receive either levetiracetam, lamotrigine, or sodium valproate. (392 in each arm; 1176 in total.)
- EpiNet-*First* Trial 5 Patients with seizures of unknown nature and sodium valproate is deemed unsuitable (e.g. in women of childbearing age), then patients with seizures of unknown nature will be randomised to receive either levetiracetam or lamotrigine. (332 in each arm; 664 in total.)

### 9.3 Outcome Measures

See section 4.

### 9.4 Interim Monitoring and Analyses

Recruitment rates will be reviewed regularly, and annual progress reports regarding patient recruitment will be prepared and forwarded to the Independent Advisory group and appropriate ethics committees. No interim analysis is planned.

### 9.5 Analysis Plan

All participants who are invited to participate in EpiNet-*First* trials will be accounted for and a CONSORT statement prepared. A table summarizing the number of participants who have assessed for eligibility, registered in each trial and been randomized for participation, will be provided. Participant disposition will be presented in one or more figures.

Demographic data collected on all randomised participants will be summarized. Summaries of continuous variables which are normally distributed will be presented as means and standard deviations or medians and inter-quartiles for skewed data, while categorical variables will be presented as frequencies and percentages.

Treatment evaluations will be undertaken for each trial separately. The primary outcome will be summarised by Kaplan-Meier curves and compared between the treatment groups using the log rank test. Cox proportional hazards regression models will be used in two different ways: (i) including the treatment effect only, using treatment indicator variables (ii) including the treatment effect together with stratification factors and important baseline covariates. The impact of country effect on the treatment comparison will be controlled by considering a random effect in the regression analysis. A similar analysis strategy will be employed for the other secondary time to event outcomes. For time to treatment failure, further analysis will be undertaken to assess the two main reasons for treatment failure-inadequate seizure control and unacceptable adverse effects. To allow for possible dependence between the different withdrawal risks, cumulative incidence analyses will be presented(39).

The proportion of patients who achieve a 12 month remission by 18 months who have not changed to a different AED will be compared between treatment groups using simple chi-squared test with estimation of relative risks and 95% confidence

intervals. Logistic regression analysis will also be conducted adjusting for stratification factors and important baseline covariates.

QOL data will be analysed longitudinally to explore between treatments differences in scale scores overtime, taking account of stratification factors, baseline QOL and other important covariates. Line listings will be prepared for all serious adverse events.

A full Statistical Analysis Plan (SAP) will be developed by the project statistician prior to the final analysis of each trial. The SAP will be agreed by the TSC before being sent to the IAG for comment and approval.

**9.6 Per-Protocol Analysis / Protocol Violations**

Secondary per protocol (PP) analyses will be undertaken to assess the robustness of ITT analyses. Per protocol analyses will exclude patients who turned out not to have epilepsy, patients who were lost to follow up or for whom there is inadequate data to determine if they reached the primary endpoint, and all patients who took a different AED from the drug to which they had been randomised, before reaching the primary endpoint. Patients who were enrolled in EpiNet-First Trial 1 who turned out not to have focal seizures will be excluded from the PP analysis; similarly, patients who were enrolled in EpiNet-First Trial 2 or Trial 3 who turned out to have focal seizures (even if these evolved into generalised seizures) will also be excluded from the PP analysis. However, all patients who were included in EpiNet-First Trial 4 or Trial 5 will be included in the PP analysis if they had epilepsy, even if the exact nature of the seizures became clearer during the course of the trial.

The decision regarding which patients to exclude from the PP analysis will be made by the Trial Steering committee, who will be blinded to the treatment allocation and outcome data for each patient.

## 10. PHARMACOVIGILANCE

All Serious Adverse Events (SAE) and Reactions (SARs) or Suspected Unexpected Serious Adverse Reaction (SUSARs) will be recorded and reported as secondary endpoints of the studies. Systematic collection of all adverse events or adverse reactions will not be performed, as the trial medications are in use worldwide and side effects are well established.

All adverse events deemed important by the local investigator should be recorded in the EpiNet record. Other adverse events reported to a physician can also be recorded in EpiNet as 'Drug Side Effects' in the Treatment form at the physician's discretion. This data, however, will not be collated and reported as an end-point of the EpiNet-*First* study. Quality of Life will be used as an assessment of a patient's overall tolerance to a drug versus seizure control.

### 10.1Terms and Definitions

The Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) definitions:

**Adverse Event (AE)**

Any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.

**Adverse Reaction (AR)**

Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

**Unexpected Adverse Reaction (UAR)**

An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in:

In the case of a product with a marketing authorization, in the summary of product characteristics for that product

In the case of any other investigational medicinal product, in the investigator's brochure relating to the trial in question.

**Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)**

Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- results in death
- is life-threatening* (subject at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation; **
- results in persistent or significant disability or incapacity, or

- consists of a congenital anomaly or birth defect
- Other important medical events***

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute a Serious Adverse Event.

***Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event / experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

**10.2 Relationship to Trial Treatment**

For the purpose of pharmacovigilance reporting, all Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs) and Suspected Unexpected Serious Adverse Reactions (SUSARs) are reportable for EpiNet-*First* (see section 10.4).

For SAEs / SARs / SUSARs the assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in Table 2.

If any doubt about the causality exists the local investigator should inform the study coordination centre.

**Table 2: Definitions of Causality**

| Relationship | Description |
|---|---|
| **Unrelated** | There is no evidence of any causal relationship.<br>There is an alternative cause for the AE. |
| **Unlikely** | There is little evidence to suggest there is a causal relationship<br>(e.g. the event did not occur within a reasonable time after administration of the trial medication or other anti-epileptic medication). There is another reasonable explanation for the event (e.g. the participant's clinical |
| **Possibly** | There is some evidence to suggest a causal relationship (e.g.<br>because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the |
| **Probably** | There is evidence to suggest a causal relationship and the influence of other factors is unlikely. |
| **Almost certainly** | There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out. |

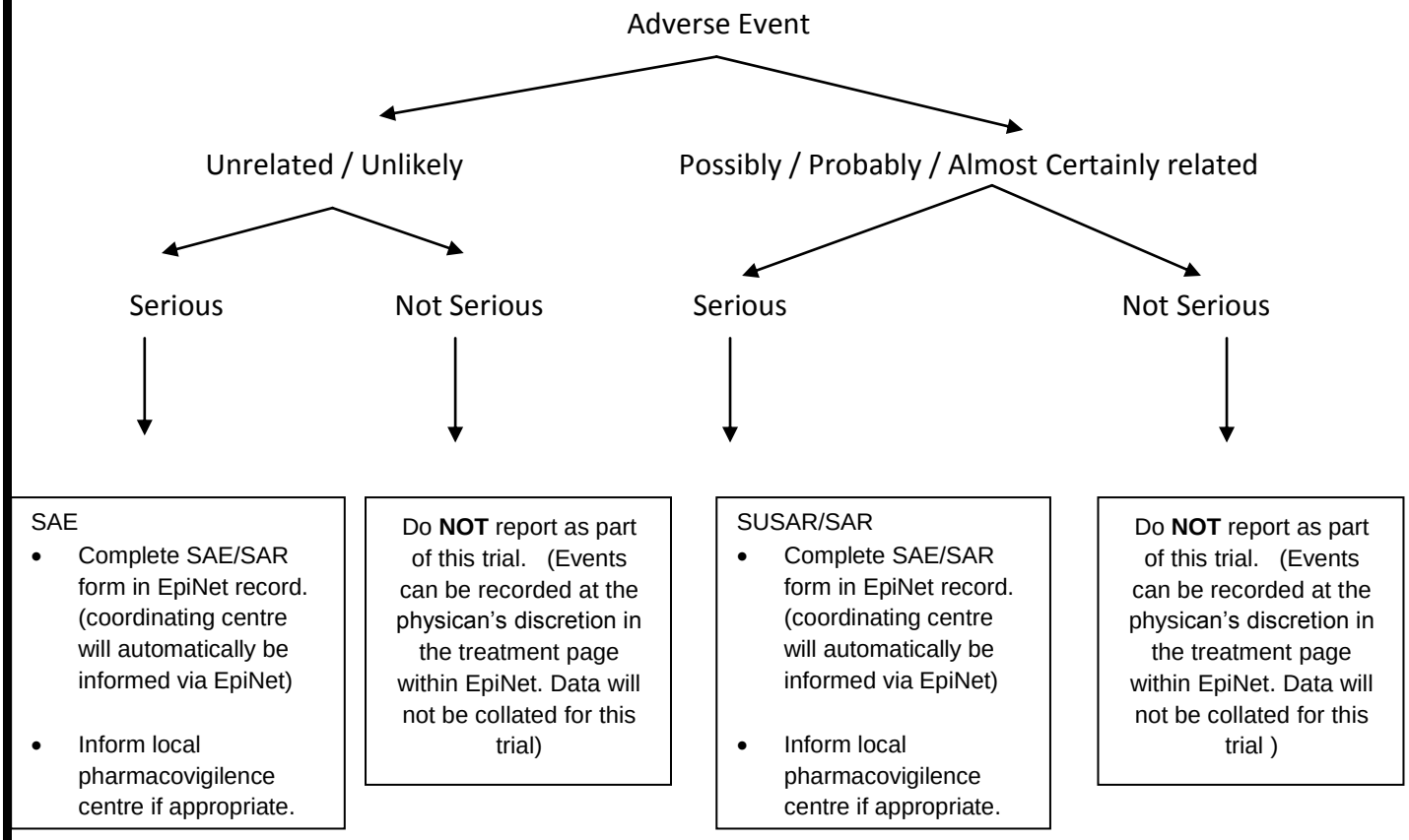
### 10.3.Expectedness

Expectedness should be assessed for all serious adverse reactions; refer to the relevant datasheet for a list of expected adverse reactions for each study treatment.

All events judged by the designated investigator as serious and **unexpected** (i.e. not listed in the relevant datasheet) and considered to be possibly, probably, or almost certainly related to the study medication, should be reported as a SUSAR.

### 10.4 .Reporting Procedures

All SAEs which occur from the time of consent until the final follow-up visit will be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the coordinating centre in the first instance. A flowchart is given below to aid in determining reporting requirements.




### 10.4.1 Include

All SAEs / SARs / SUSARs as defined in section 10.1.

It is not necessary to include:

- Medical or surgical procedures - the condition which leads to the procedure

is the adverse event

- Pre-existing disease or conditions present before treatment that do not worsen
- Situations where an untoward medical occurrence has occurred e.g. cosmetic elective surgery
- Overdose of medication without signs or symptoms
- The disease being treated or associated symptoms/signs unless more severe than expected for the patient's condition

### 10.4.2 Serious ARs/SUSARs

SAEs, SARs and SUSARs should be reported as soon as possible to the relevant local pharmacovigilence centre.

The SAE/SAR form within EpiNet will record the nature of event, date of onset, severity, corrective therapies given, outcome and causality. EpiNet will automatically alert the co-ordinating centre of the SAE/SAR.

The responsible investigator should assign the causality of the event. Additional follow-up information should be recorded if the reaction has not resolved at the time of reporting

### 10.4.3 Reporting of Pregnancy

Any pregnancy which occurs during the study should be reported to the coordinating centre using the 'Other important medical information' form within EpiNet. EpiNet will automatically alert the coordinating centre of the pregnancy. All pregnancies that occur during treatment need to be followed up as per usual care. Any SAR experienced during pregnancy must be reported on the SAE/SAR form within EpiNet.

The investigator will follow usual care and notify the participant of the possible effect to the foetus. Appropriate Obstetric care should be arranged.

### 10.4.4 Reporting of Deaths

All deaths that occur between the time of consent and the final follow-up visit should be reported to the coordinating centre using the Serious Adverse Events form in the EpiNet record. In addition, the relevant section on the 'Other important medical information' form should also be completed.

### 10.4.5 Reporting of Hospital Admissions

SAEs resulting in hospital admissions will be reported.

## 10.5 Follow-up After Adverse Events

All adverse events should be followed until satisfactory resolution or until the investigator

responsible for the care of the participant deems the event to be chronic or the patient to be stable.

When reporting SARs and SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes:

resolved;
resolved with sequelae (specifying with additional narrative);
not resolved / ongoing;
ongoing at final follow-up;
fatal or
unknown.

### 10.6 Responsibilities – Investigator

The Investigator is responsible for reporting SARs that are observed or reported during the study.

All SARs must be reported immediately by the investigator by completing the SAE/SAR page within EpiNet. The coordinating centre will be automatically notified via an alert sent via EpiNet.

All pregnancies, deaths or SAEs should be reported as described in sections

10.4.4, 10.4.5 and
10.4.6.

**Minimum information required for SAR reporting:**

- Study identifier
- Study centre
- Patient number
- A description of the event
- Date of onset
- Current status
- Whether study treatment was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study treatment

(i) The SAE/SAR form within EpiNet should be completed by a designated investigator, or nominee. The investigator should assess the SAE for the likelihood that it is a response to the investigational medicinal product or other anti-epileptic drug. An automatic alert within EpiNet will notify the coordinating centre of the event. The initial report shall be followed by detailed reports as appropriate.

(ii) The responsible investigator must notify local regulatory authorities (if required per standard local governance procedures).

(iii) In the case of an SAR the participant must be followed-up until clinical recovery is complete, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.

(iv) Follow-up information is noted within EpiNet. Extra annotated information and/or copies of test results may be provided separately.

(v) The patient should be identified by subject number, date of birth and initials only. The patient's name should not be used in any correspondence.

## 11. ETHICAL CONSIDERATIONS

### 11.1Ethical Considerations

The study will abide by the principles of the World Medical Association Declaration of Helsinki (1964) and subsequent amendments.

The specific ethical issues relating to participation in this trial are considered to be:

**Informed consent in a paediatric population:** The parent or legal representative of the child will have an interview with the investigator, or a delegated member of the investigating team, during which opportunity will be given to understand the objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted. They will be provided with written information and contact details of a member of the research team at the centre, from whom further information about the trial may be obtained, and will be made aware of their right to withdraw the child from the trial at any time without the child or family being subject to any detriment in the child's treatment. Children will receive information, according to their capacity of understanding, about the trial and its risks and benefits and their assent will be obtained, where appropriate.

### 11.2 Ethical Approval

The trial protocol and information/consent form must be approved by each site's ethics committee and a copy should be forwarded to the coordinating centre before patients are recruited at that site. The ethics committee must be appropriately constituted according to ICH GCP Guidelines.

### 11.3 Informed Consent Process

Informed consent is a process initiated prior to an individual agreeing to participate in a trial and continues throughout the individual's participation. Informed consent is required for all patients participating in EpiNet trials. In obtaining and documenting informed consent, the investigator should comply with applicable regulatory requirements and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to patients by staff with experience in obtaining informed consent. Patient Information Sheet and Consent forms (PISC), describing in detail the trial interventions / products, trial procedures and risks will be approved by an independent ethical committee (IEC) and the patient (parent/legal representative in the case of minors) will be asked to read and review the document. Upon reviewing the document, the investigator will explain the research study to the patient (parent/legal representative in the case of minors). This information will emphasise that participation in the trial is voluntary and that the participant may withdraw from the trial at any time and for any reason. All participants will be given

opportunity to ask any questions that may arise, and will be given the opportunity to discuss the study with their surrogates, and time to consider the information prior to agreeing to participate. A contact point where further information about the trial may be obtained will be provided.

The patient (parent or legal representative in the case of minors) will then sign and date the informed consent document. Both the person taking consent and the participant (parent or legal representative in the case of minors) must personally sign and date the form. A copy of the informed consent document will be given to the patient (parent or legal representative in the case of minors) for their records. The original copy of the signed consent form will be retained in the investigator site file. Participants will have as long as they require to consider their decision to join the trial or not. The participant may, without being subject to any resulting detriment, withdraw from the trial at any time by revoking the informed consent (Similarly, the parent or legal representative may withdraw a minor under the same conditions). The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study.

The right of the participant or their parent/ legal representative to refuse consent for themselves or the minor to participate in the trial without giving reasons must be respected. After the participant has entered the trial, the clinician must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. However, the reason for doing so should be recorded and the patient will remain within the trial for the purpose of follow-up and data analysis. Similarly, the participant or their parent / legal representative remains free to withdraw the patient at any time from the protocol treatment and/or trial follow-up without giving reasons and without prejudicing the further treatment of the participant.

### 11.3.1 Assent in minors

If capable, and under appropriate circumstances, and according to local requirements, minors should be approached to provide assent by a member of the research team with experience with minors. Appropriate Patient information Sheet and Assent forms, describing (in simplified terms) the details of the trial intervention/product, trial procedures and risks should be used. The minor should personally write their name and date the assent form, which is then signed by the parent/legal representative and the researcher.

Assent forms do not substitute for the consent form signed by the patient's legally acceptable representative. Assent should be taken where appropriate, however the absence of assent does not exclude the patient provided consent has been obtained from the parent/legal representative.

### 11.4 Study Discontinuation

In the event that the study is discontinued, participants will be treated according to usual standard clinical care. The process for participants who withdraw early from trial treatment or from the trial completely is described in section 5.3

## 12. TRIAL MONITORING

### 12.1 Risk Assessment

A risk assessment has been performed for the EpiNet-*First* trials. The outcome of the EpiNet-*First* specific risk assessment is that EpiNet-*First* trials have been judged as **Low risk** clinical trials. This level of risk has determined the approach to trial monitoring described in this section.

Risks can be assessed according to the following categories:

***Type A*** *'no higher than that of standard medical care';*
***Type B*** *'somewhat higher than that of standard medical care';*
***Type C*** *'markedly higher than that of standard medical care'.*

EpiNet-*First* trials are pragmatic trials that use authorised drugs within the terms of marketing authorisation. Based on this marketing authorisation status of the medicines being investigated, EpiNet-*First* trials are categorised as ***Type A*** *with* ***"no higher than the risk of standard medical care".*** This level of risk informs the risk assessment, regulatory requirements, nature and extent of the monitoring, and the management processes used in the trial.

A detailed risk assessment was previously also performed for the SANAD-11 trial, in accordance with local practice; in conducting this risk assessment, the contributors considered potential patient, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur.

The outcome of this risk assessment was that the SANAD-11 trials were also considered to be Low risk.

### 12.2 Data Capture Methods

Data capture will be by entry of data directly into the EpiNet database. Data may be entered either by investigators or research assistants, but it will need to be verified by an accredited investigator at the study site before it will be accepted into the definitive research database. Forms will be 'parked' until they have been verified.

#### 12.2.1 EpiNet record

The on-line EpiNet record is the primary data collection instrument for the study. All data that is marked as mandatory in the EpiNet record must be recorded. Any data that is mandatory but is missing must be explained. Non-mandatory fields can be entered if the investigator believes this will be helpful for clinical purposes.

#### 12.2.2 Patient Completed Data

The participant initials and randomization / subject number should be clearly labelled on all paper documents e.g. seizure diaries.

Patient seizure diaries will be presented at each follow up visit and data from them will be entered into the EpiNet database. Patient seizure diaries should be photocopied and copies given to the patient. The original should be kept at the site as they are a source document.

Centres will be required to forward to the coordinating centre copies of the informed consent documents and seizure diaries on a select number of patients. The entries made in the EpiNet records will be checked against these documents. The complete EpiNet records for these patients will be checked in detail to ensure that the data is valid.

At least one record will be checked from each centre.

### 12.3 Source Documents

In order to resolve possible discrepancies between information appearing in the EpiNet record and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the EpiNet record. Data recorded in the EpiNet record should be consistent and verifiable with source data in source documents *other* than the EpiNet record (e.g. seizure diary).
Identified source documents other than the EpiNet record for this trial are:

- Hospital Records
- Hard copy questionnaires
- Participant seizure diaries
- Printouts from automated instruments (EEG & Imaging)

Therefore, for data where no prior record exists, and which is recorded directly in the EpiNet record, the EpiNet record will be considered the **source document**, unless otherwise indicated by the investigator.
The fact that the patient is participating in a clinical trial (including allocated treatment arm) should be recorded in the patient's medical record. Date(s) of obtaining informed consent and date(s) of provision of patient information, and randomisation number should be recorded in the notes chronologically.

### 12.4 Data Monitoring at the coordinating centre

Data will be reviewed centrally by an independent data analyst to look for unusual patterns which might indicate erroneous or falsified data. Data from each centre will be compared with that obtained from other centres(40). Data on selected patients will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Any suspect data will be returned to the site in the form of data

queries. Data queries will be produced at the coordinating centre from the trial database and sent either electronically or via e-mail to a named individual at an approved centre. Sites will respond to the queries providing an explanation/resolution to the discrepancies.

### 12.5 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Documents relating to patients will be labelled with the patient's initials and unique trial screening and / or randomisation number. Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

The coordinating centre require the transfer of identifiable data solely to verify that appropriate informed consent is obtained on selected patients.

### 12.6 Records Retention

The investigator at each investigational site must make arrangements to store the essential trial documents, including the Investigator Site File until the EpiNet-*First* steering committee informs the investigator that the documents are no longer to be retained, or for a maximum period of 10 years after study completion (whichever is soonest).

## 13. INDEMNITY

EpiNet-*First* is sponsored by The EpiNet steering group. The EpiNet steering group does not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity.

## 14. FINANCIAL ARRANGEMENTS

### 14.1. Per patient payments

There is no funding for per patient payments when participants are recruited or for follow up visits.

## 15. TRIAL COMMITTEE

### 15.1 Trial Steering Committee (TSC)

The Trial Steering Committee will comprise members of the EpiNet steering committee plus a biostatistician and the principal Investigators from several of the countries in which the EpiNet trials will be run. The role of the TSC is to provide overall supervision for the trial. The ultimate decision for the continuation of the trial lies with the TSC.

### 15.2 Independent Advisory Group (IAG)

The Independent Advisory Group will consist of independent experts in the field of clinical trials in epilepsy.

The IAG will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IAG will first convene prior to the start of recruitment and will then define frequency of subsequent meetings.

The IAG will provide a recommendation to the Trial Steering Committee concerning the continuation of the study.

## 16. TRIAL REGISTRATION AND PUBLICATION

This trial will be prospectively registered on a Clinical Trial Registry.

The results from different centres will be analysed together and published as soon as possible. Individual Clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the TSC.

The TSC will form the basis of the Writing Committee and advise on the nature of publications. The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) will be respected. All publications shall include a list of participants, and if there are named authors, these should include the trial's Chief Investigator(s), Statistician(s) and Trial Manager(s) involved at least. If there are no named authors (i.e. group authorship) then a writing committee will be identified that would usually include these people, at least. The ISRCTN (International Standard Randomised Controlled Trial Number) allocated to this trial should be attached to any publications resulting from this trial.

The members of the TSC and IAG should be listed with their affiliations in the Acknowledgements/Appendix of the main publication.

## 17. PROTOCOL AMENDMENTS

Any Amendments to this protocol will be implemented at each study site after approval from the local ethics committee has been obtained.

### 17.1 Version

Version 1 dated - 15th April 20
Version 2 dated - 17th June 2014

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## 19 DOCUMENTS SUPPLEMENTARY TO THE PROTOCOL

The following supplementary documents will accompany the protocol and are separately updated and version controlled:

- Patient information sheet and consent form (age-specific versions)
- Summary of Products Characteristics (Carbamazepine, Lamotrigine, levetiracetam, Valproate)
- Quality of Life in Epilepsy-31(QOLIE 31)
- Quality of Life in Epilepsy-48(QOLIE 48)