A pragmatic randomised controlled trial comparing the effectiveness and cost effectiveness of levetiracetam and zonisamide versus standard treatments for epilepsy: a comparison of Standard And New Antiepileptic Drugs (SANAD-II)

Trial Protocol

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www.sanad2.org.uk

Study Sponsors:

The Walton Centre NHS Foundation Trust
Lower Lane
Fazakerley
Liverpool
L9 7LJ

University of Liverpool
Research Business Services
Foresight Building
3 Brownlow Street
Liverpool
L69 3GL

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CTRC
Clinical Trials Research Centre

NHS
National Institute for Health Research

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Protocol Approval
Authorised by Chief Investigator:

Signature: _____ **Date:** 29/11/18

Professor A Marson
Professor of Neurology
University of Liverpool
Department of Molecular and Clinical Pharmacology
Clinical Sciences Centre
Lower Lane
Liverpool L9 7LJ
Tel: 0151 529 5770
Fax: 0151 529 5466
E-mail: a.g.marson@liv.ac.uk

Authorised by Lead Statistician:

Signature: Cath Tudur Smith **Date:** 5/12/18

Professor Catrin Tudur Smith
Professor in Medical Statistics
Department of Biostatistics
University of Liverpool
Block F, Waterhouse Building
1-5 Brownlow Street
Liverpool L69 3GL
Tel: 0151 794 9754
E-mail: cat1@liverpool.ac.uk

Authorised on behalf of the Sponsor:

Signature: Martin Wilby **Date:** 14th Dec 2018

Mr Martin Wilby , Clinical Director of Research, Development and Innovation
The Walton Centre NHS Foundation Trust
Lower Lane
Fazakerley
Liverpool L9 7LJ
Tel: 0151 529 5667
[illegible]waltoncentre.nhs.uk

Signature: _____ **Date:** 10 Dec 18

Mr Alex Astor
Head of Research Support – Health and Life Sciences
University of Liverpool
Research Support Office
2nd Floor Block D Waterhouse Building
3 Brownlow Street
Liverpool
L69 3GL

General Information

This document describes the SANAD II trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients; every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant 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.

Incidence of protocol non-compliance, whether reported prospectively (e.g. where a treatment cannot be administered on a scheduled date as a result of public holidays) or retrospectively noted (e.g. as a result of central monitoring) are recorded as protocol deviations, the incidence of which are monitored and reported to trial oversight committees.

Statement of Compliance

This study will be carried out in accordance with the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996) amendments and will be conducted in compliance with the protocol, CTRC Standard Operating Procedures and EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 as amended.

Relationship Statements

The UK Clinical Research Collaboration (UKCRC; www.ukcrc.org) is a partnership organisation working to establish the UK as a world leader in clinical research. Following a review by an international panel, the Clinical Trials Research Centre (CTRC) at the University of Liverpool has been assessed as reaching the highest quality standard required by the UKCRC and achieved full UKCRC registration.

The CTRC encompasses clinical trials activity in areas including medicines for children (The Medicines for Children Research Network Clinical Trials Unit; MCRN CTU), cancer (The Liverpool Cancer Trials Unit; LCTU), epilepsy, oral health and obstetrics and gynecology (http://www.ctrc.org.uk/). All CTRC activities are underpinned by methodological rigour, a modern data management system, similar technical requirements and a common set of standard operating procedures.

The CTRC epilepsy portfolio is part of the Liverpool Epilepsy Research Group (LERG), which has an international reputation for undertaking clinically-based research in epilepsy, and the group's portfolio ranges from fundamental science through to health service research. The Liverpool group has lead the three largest randomized controlled trials in epilepsy to date, including SANAD I, MESS and the MRC antiepileptic drug withdrawal study.

The NIHR Medicines for Children Research Network (MCRN) is part of the National Institute for Health Research Clinical Research Network.

Contact Details: Institutions

Co-Sponsors:	Trial Management and Monitoring:	DNA archive
The Walton Centre NHS Foundation Trust Research Governance Office Lower Lane Fazakerley Liverpool L9 7LJ Tel: 0151 525 5667 E-mail: dave.watling@thewaltoncentre.nhs.uk University of Liverpool Research Support Office 2nd Floor, Block D Waterhouse Building 3 Brownlow Street Liverpool L69 3GL Tel: 0151 794 8739 E-mail: sponsor@liv.ac.uk	Clinical Trials Research Centre (Epilepsy Lead: Professor Tony Marson) c/o Liverpool Epilepsy Research Group Coordinating Centre University of Liverpool Department of Molecular and Clinical Pharmacology Clinical Sciences Centre Lower Lane Liverpool L9 7LJ Tel: 0151 529 5464 Fax: 0151 529 5466 E-mail: sanad2@liv.ac.uk	Wolfson Centre for Personalised Medicine Department of Molecular & Clinical Pharmacology University of Liverpool Block A: Waterhouse Buildings 1-5 Brownlow Street Liverpool L69 3GL Tel: 0151 795 5391 Fax: 0151 794 5059 E-mail: g.sills@liv.ac.uk
Other Medical or Technical Departments and/or Institutions (1):	**Other Medical or Technical Departments and/or Institutions (2)**	**Other Medical or Technical Departments and/or Institutions (3)**
Clinical Trials Research Centre University of Liverpool Institute of Child Health Alder Hey Children's NHS Foundation Trust Liverpool L12 2AP Tel: 0151 795 8751 Fax: 0151 795 8770 E-mail: jogard@liverpool.ac.uk	Centre for Health Economics and Medicines Evaluation Institute of Medical and Social Care Research Bangor University Dean Street Gwynedd North Wales LL57 1UT Tel: 01248 382950 Fax: 01248 383982 E-mail: d.a.hughes@bangor.ac.uk	

Contact Details: Individuals

Individuals Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	Chief Investigator (CI):
Mr Martin Wilby, Clinical Director of Research, Development and Innovation The Walton Centre NHS Foundation Trust Lower Lane Fazakerley Liverpool L9 7LJ Tel: 0151 529 5667 E-mail: malcolm.steiger@thewaltoncentre.nhs.uk Mr Alex Astor Head of Research Support – Health and Life Sciences University of Liverpool Research Support Office 2nd Floor Block D Waterhouse Building 3 Brownlow Street Liverpool L69 3GL astor@liverpool.ac.uk	Professor Tony Marson Professor of Neurology University of Liverpool Department of Molecular and Clinical Pharmacology Clinical Sciences Centre Lower Lane Liverpool L9 7LJ Tel: 0151 529 5770 Fax: 0151 529 5466 E-mail: a.g.marson@liv.ac.uk
Medical Expert who will Advise on Protocol Related Clinical Queries (In CI absence):	**Medical Expert who will Evaluate SAE Reports (In CI absence):**
Dr Richard Appleton Consultant Paediatric Neurologist Roald Dahl EEG Department Paediatric Neurosciences Foundation Alder Hey Children's NHS Foundation Trust Eaton Road Liverpool L12 2AP Tel: 0151 252 5851 / 5375 Fax: 0151 252 5152 E-mail: richard.appleton@alderhey.nhs.uk	Dr Richard Appleton Consultant Paediatric Neurologist Roald Dahl EEG Department Paediatric Neurosciences Foundation Alder Hey Children's NHS Foundation Trust Eaton Road Liverpool L12 2AP Tel: 0151 252 5851 / 5375 Fax: 0151 252 5152 E-mail: richard.appleton@alderhey.nhs.uk

The contact details of other individuals involved in the trial are detailed in the Trial Oversight Committee Membership document.

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Glossary

ABPI	Association of the British Pharmaceutical Industry
AE	Adverse Event
AED	Anti-epileptic Drugs
AR	Adverse Reaction
CCRN	Comprehensive Clinical Research Network
CI	Chief Investigator
CRF	Case Report Form
CR-UK LCTU	Cancer Research UK Liverpool Cancer Trials Unit
CSRI	Client Service Receipt Inventory
CTRC	Clinical Trials Research Centre
CTU	Clinical Trials Unit
GP	General Practitioner
HES	Hospital Episode Statistics
HR	Hazard Ratio
HTA	Health Technology Assessment Programme
IDSMC	Independent Data and Safety and Monitoring Committee
IEC	Independent Ethical Committee
ILAE	International League Against Epilepsy
IMP	Investigational Medicinal Product
ITT	Intention to Treat
LERG	Liverpool Epilepsy Research Group
MCRN CTU	Medicines for Children Research Network Clinical Trials Unit
MREC	Multi-centre Research Ethics Committee
NI	Non-Inferiority
NIHR	National Institute for Health Research
NIHR CRN	National Institute for Health Research Clinical Research Network
PI	Principal Investigator
QALY	Quality-Adjusted Life Year
QOL	Quality of Life
R&D	Research & Development
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Data Verification
SPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction

1 PROTOCOL SUMMARY

Title:	A pragmatic randomised controlled trial comparing the effectiveness and cost effectiveness of levetiracetam and zonisamide versus standard treatments for epilepsy: a comparison of Standard And New Antiepileptic Drugs (SANAD-II)
Phase:	IV
Population:	About 1500 patients (990 with focal onset seizures and 520 with generalised onset seizures or difficult to classify seizures) **Inclusion Criteria:** • Aged 5 years or older • Two or more spontaneous seizures that require antiepileptic drug treatment • Untreated and not previously treated with antiepileptic drugs, except emergency treatment in the past 2 weeks • Antiepileptic drug monotherapy considered the most appropriate option • Willing to provide consent (patients parent/legal representative willing to give consent where the patient is aged under 16 years of age or is lacking capacity to consent) **Exclusion Criteria:** • Provoked seizures only (e.g. alcohol or drug-induced) • Acute symptomatic seizures only (e.g. within 1 month from acute brain haemorrhage or brain injury or stroke) • Currently treated with antiepileptic drugs • Progressive neurological disease (e.g. known brain tumour)
Study Centres and Distribution:	UK NHS out-patient epilepsy, general neurology and paediatric (epilepsy and general) clinics
Study Duration:	Minimum participant duration 2 years Maximum participant duration 5.5 years (about 6.5 years for early recruits in Arm A)
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

OR

Levetiracetam

OR

Zonisamide

Generalised onset seizure / difficult to classify seizure participants

Levetiracetam

OR

Valproate

Primary Outcome:

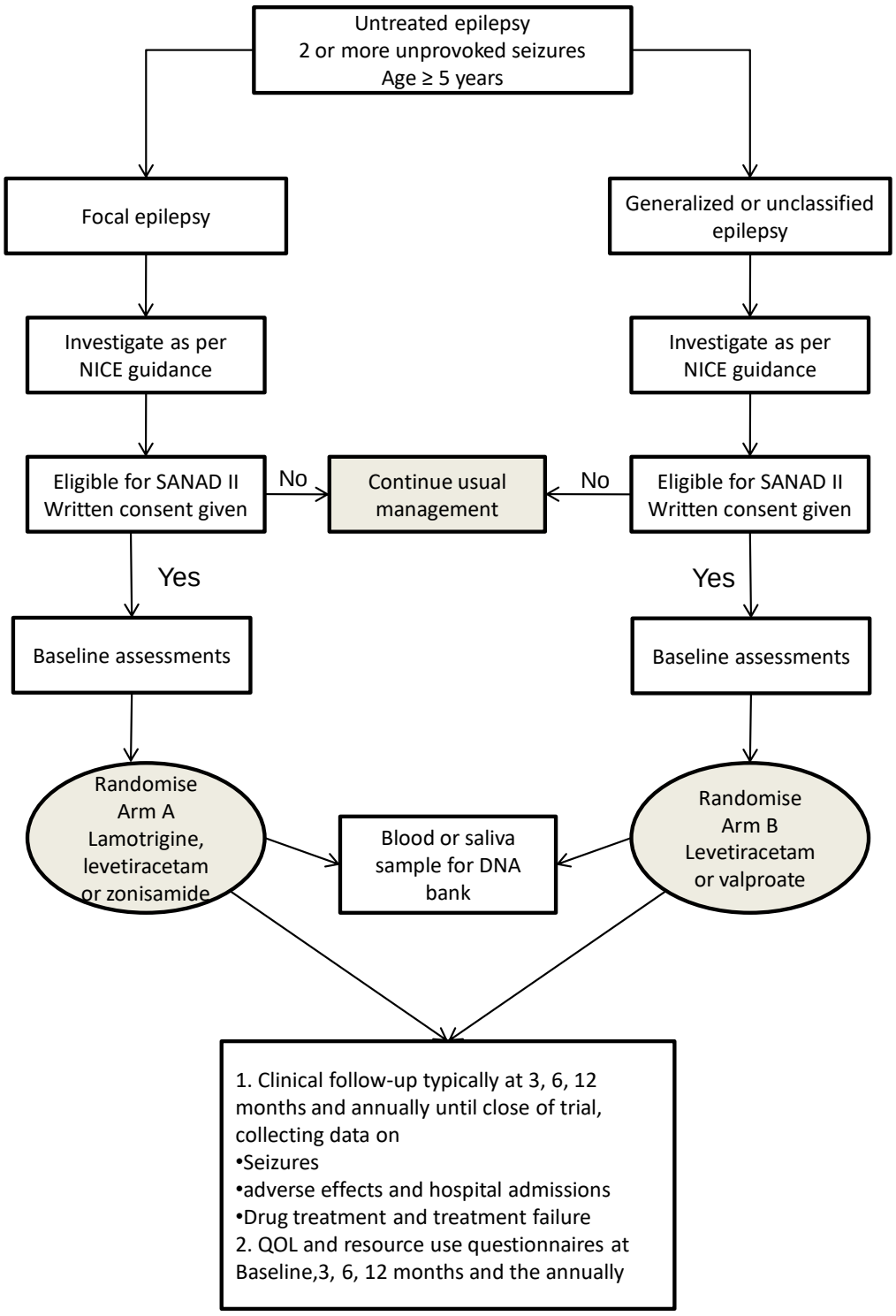
Time to 12 month remission - measured using data recorded in participant seizure diaries and seizure data collected at all follow up visits

Secondary Outcomes:

- *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**
- *Adverse events**
- *Quality Of Life (QOL)**
- *Health economic outcomes**

* Measured using information provided by the patient and clinicians

Schematic of Study Design:



2 BACKGROUND INFORMATION

2.1 Definitions (ILAE Glossary)

For SANAD II, epileptic seizures will be classified according to the International League Against Epilepsy (ILAE) classification of seizures that was published in 1981(1). Epileptic syndromes will be classified according the ILAE classification published in 1989(2).

Focal seizure - A seizure whose initial semiology indicates, or is consistent with, initial activation of only part of one cerebral hemisphere. Seizure types include simple partial seizures, complex partial seizures, and secondary generalised tonic clonic seizures.

Generalised seizure - A seizure whose initial semiology indicates, or is consistent with, more than minimal involvement of both cerebral hemispheres. Seizure types will include absence seizures, myoclonic seizures, and generalised tonic clonic seizures.

Unclassified seizures are those that the clinician cannot classify as focal or generalised in onset. NB. Generalised epilepsies rarely present after the age of 25 years.

2.2 Introduction

Epilepsy is a common neurological condition and up to 3% of people will experience seizures at some time in their lives (3). 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 (4, 5). Antiepileptic drugs (AEDs) are the mainstay of treatment and may have to be taken for life. The ultimate goal of treatment is to maximise quality of life by eliminating seizures at drug doses that do not cause side effects. However, for many patients there is a necessary trade-off between effective seizure control and side effects, which can diminish quality of life.

Over the past 20 years, a number of new drugs have become available for the treatment of epilepsy. These new drugs have been approved for NHS use on the basis of information from short term trials. These trials do not provide information about the longer term outcomes which inform decisions made by doctors and patients, nor do they provide any useful health economic data.

SANAD-I began in 1999 and compared the effectiveness and cost effectiveness of standard and new treatments that were available at that time (6, 7). SANAD-I identified lamotrigine (a new drug) as an effective and cost-effective first-line treatment for patients with a focal epilepsy, and confirmed that valproate (a standard treatment) should remain a first-line drug for patients with a generalised epilepsy or seizures that clinicians find difficult to classify. Since SANAD-I, a number of newer treatments have become available, the most promising of which are levetiracetam and zonisamide.

2.3 Rationale

Arm A (focal epilepsy) of SANAD-II will compare lamotrigine, levetiracetam and zonisamide in patients with untreated focal onset seizures. While the focal epilepsies are further classified into a number of syndromes (2) largely according to aetiology and site of onset, it

has been common practice to recruit a heterogeneous population with focal onset seizures into epilepsy trials. There are currently no reliable data that indicate whether relative treatment responses differ among the focal epilepsies, indeed prognostic modelling of data from SANAD-I suggests that treatment effects are consistent across focal epilepsy syndromes as currently classified (6, 8). In SANAD-II, we propose to recruit patients with focal onset seizures irrespective of syndrome, which will allow further opportunity to investigate treatment effects and factors, including syndrome, that influence those effects.

Carbamazepine has long been considered a first line treatment for patients with focal onset seizures (9). Prior to SANAD-I (6, 7) trials comparing lamotrigine and carbamazepine monotherapy had been sponsored by industry with a view to informing drug-licensing decisions. The trials undertaken had been of less than 12 months duration, and hence unable to provide data regarding long-term outcomes. In addition, quality of life and health economic outcomes had not been adequately assessed. A systematic review of such trials (10) comparing lamotrigine and carbamazepine, showed that lamotrigine was significantly better tolerated than carbamazepine, but for the outcome of time to 6-month remission there was a non-significant trend in favour of carbamazepine.

In SANAD-I, Arm A primarily recruited patients with focal onset seizures who were randomly allocated to treatment with carbamazepine, lamotrigine, topiramate, gabapentin or oxcarbazepine (6). Topiramate and gabapentin were identified as poor first line treatments, gabapentin because of inadequate seizure control and topiramate because of poor tolerability. Lamotrigine was significantly less likely to fail (joint primary outcome time to treatment failure) than carbamazepine. A competing risks analysis for time to treatment failure showed that there were significantly fewer treatment failures on lamotrigine due to lack of tolerability, while treatment failure events for lack of efficacy were similar to those for carbamazepine. In terms of seizure control, for time to 12 month remission (joint primary outcome) lamotrigine was similar to, and indeed non-inferior to carbamazepine. The health economic analysis indicated that lamotrigine is a cost-effective alternative to carbamazepine. Lamotrigine was also found to be better tolerated and of similar efficacy to carbamazepine in patients with seizures following stroke (11), while another trial in the elderly found similar treatment withdrawal rates, with a trend in favour of lamotrigine for tolerability and a trend in favour of carbamazepine for efficacy. This body of evidence supports the consideration of lamotrigine as the standard treatment against which new drugs should be compared for patients with focal onset seizures, as has been suggested by commentators (12). In SANAD-II, lamotrigine will be the standard drug against which levetiracetam and zonisamide are compared for patients with focal onset seizures.

Levetiracetam is a well established antiepileptic drug in the UK, commonly used as a first line add-on treatment for children and adults with focal onset seizures and it is also licensed for use as monotherapy. A Cochrane review of 4 short term randomised placebo controlled add-on trials in patients (n=1023) with drug refractory focal onset seizures demonstrated efficacy and tolerability when levetiracetam is used as an add-on treatment (13).

Levetiracetam has also been assessed as monotherapy for patients with focal onset seizures, but trials published to date have been regulatory studies that fail to inform clinical practice or policy. A short term trial (576 patients) comparing levetiracetam and carbamazepine monotherapy in patients with focal onset seizures (14) found no difference in

terms of the proportion of patients that were seizure free for 6-months. The results met an a-priori definition of non-inferiority, and the drugs were similar in terms of tolerability. Based largely upon the results of this trial, levetiracetam has been granted a license for monotherapy in the UK for patients with focal onset seizures. 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) but is yet to be published in full. Although this trial recruited 1688 patients, they were only followed up for a maximum of 12 months, so again 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. We will negotiate for access to individual patient data from these two trials so that they can be included in a meta-analysis, which will be undertaken as part of a programme of work currently funded by an NIHR programme grant. A further small trial (39 participants) that compared levetiracetam and oxcarbazepine in children with the syndrome of benign epilepsy with centro-temporal spikes (a focal epilepsy, thought to be of genetic aetiology) found no difference between these drugs for efficacy (15).

Zonisamide is a drug that has been available for many years in Japan and other countries in South East Asia where it is commonly used both as initial monotherapy and as an add-on treatment. Zonisamide has more recently been licensed for use in EU countries and in the USA. A Cochrane review of 4 short term randomised placebo controlled trials (n=850) summarised the evidence for efficacy and tolerability of zonisamide when used as an adjunctive treatment for patients with refractory focal onset seizures (16). An underpowered regulatory trial (n=167) (17) suggested efficacy of zonisamide monotherapy against historical controls as monotherapy and a pivotal monotherapy trial comparing zonisamide and carbamazepine monotherapy is due to report in the next few months, and we will pursue the date to include in a network meta-analysis. Numerous observational studies have also been published in full or as abstracts at academic meetings.

There is an urgent need to assess the clinical and cost-effectiveness of levetiracetam and zonisamide for focal onset seizures. Given the absence of any data regarding their long-term effectiveness this cannot be done within the context of a meta-analysis using indirect comparison and a longer term randomised controlled trial such as SANAD-II is required.

Arm B (generalised or unclassified epilepsy) of SANAD-II will compare levetiracetam and valproate in patients with generalised onset seizures or seizures that are difficult to classify. Patients with generalised onset seizures represent a group of syndromes, most of which are currently classified as one of the idiopathic generalised epilepsies (2), which are largely classified according to seizure type and age of onset. Syndromes include juvenile myoclonic epilepsy, childhood absence epilepsy, juvenile absence epilepsy and generalised epilepsy with tonic-clonic seizures on awakening. While these differing syndromes are recognised, there is currently no reliable evidence that relative treatment responses differ among these syndromes, indeed prognostic modelling of data from SANAD-I indicates that relative treatment responses are consistent across syndromes. It is also important to highlight that it is often difficult to declare the precise epilepsy syndrome that the patient has at the time point (typically the diagnosis of epilepsy) when a decision to start treatment is made, even

though the clinician has a description of definite seizures and the patient has had an EEG which shows generalised spike and wave changes. This is highlighted by the large subgroup of patients (38%) in SANAD-I classified as having an idiopathic generalised epilepsy with the clinician still being unable to specify the precise syndrome. The clinician will often become more confident about the precise syndrome with the passage of time and the description of further seizures should they occur. As in SANAD-I, we propose that patients enter Arm B of the trial based upon a classification of seizures (generalised onset or difficult to classify), with patients further classified by syndrome where and when such a syndromic diagnosis can be made. The influence of seizure type and syndrome upon treatment outcome can then be investigated in prognostic models.

Fewer randomised controlled trials have been undertaken to assess the comparative effects of antiepileptic drugs in patients with generalised onset seizures, or in those with seizures that are difficult to classify, even though these individuals represent over one third of people with epilepsy. Valproate has for some time been recommended as a first line treatment for such patients (9), but without evidence from RCTs to support this recommendation. A number of Cochrane reviews compared valproate with other antiepileptic drugs including carbamazepine (18), and phenytoin (19), but due to problems with power and epilepsy classification, none have showed an advantage for valproate. In Arm B of SANAD-I (7), 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. A more recently published double blind trial compared valproate, lamotrigine and ethosuximide for childhood and juvenile absence epilepsy (20). The trial duration was short with a primary outcome of treatment failure after 16 weeks therapy. Both valproate and ethosuximide were significantly superior to lamotrigine for this outcome. There were fewer failures on valproate than ethosuximide, but the difference was not statistically significant. This body of evidence supports valproate remaining a first line treatment.

Valproate however remains a difficult drug for women of childbearing potential as it is associated with a higher rate of teratogenicity than alternatives (major malformation rate ~8%) (21). 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 (22). Lamotrigine has a similar rate of major malformations (3-4%) as other standard drugs such as carbamazepine, although there are reports of high doses of lamotrigine being associated with higher rates of major malformations (21). 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. Consequently, women of childbearing potential have a difficult decision to make when starting treatment, because whatever drug they choose there is a high probability they will be taking it at the time they decide to start a family. Their options include valproate, a drug of proven effectiveness but higher rates of teratogenicity; lamotrigine, a drug of inferior effectiveness but safer in pregnancy; levetiracetam a drug of unproven effectiveness but with preliminary data suggesting safety in pregnancy. We urgently need information about the comparative effectiveness of valproate and levetiracetam to better inform this decision. Given the proven superiority of valproate over other treatments for generalised seizures and the fact that many women still opt for this drug, valproate will be the standard comparator in SANAD-II for patients with generalised onset seizures and seizures that are difficult to classify, including women of childbearing potential. Patients with seizures that are difficult to

classify are included here as they are thought best treated with drugs effective against a broad range of seizure types such as valproate.

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 (23). 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 (24). 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.

This body of evidence provides data to support levetiracetam as a potential first-line treatment for patients with generalised onset seizures and seizures that are difficult to classify. Levetiracetam is becoming increasingly assimilated into common usage and it is important that its long-term effectiveness is assessed, particularly to inform decisions made by women of child-bearing potential. Again, the absence of any long-term outcome data preclude any assessment in the context of a meta-analysis using indirect comparisons. A long-term trial such as SANAD II is required.

SANAD-II will essentially be two randomised controlled trials run in parallel this is justified as we urgently need answers regarding relative effectiveness of treatments in these two broad populations of patients. There will be economy of scale given that the protocols and data structure are almost identical and that the same group of collaborators will be recruiting patients to both trials. There will be no competition for patients between Arm A (focal epilepsy) and Arm B (generalised epilepsy) as the inclusion criteria are mutually exclusive.

2.4 Outcomes

Arm A - To compare the clinical and cost-effectiveness of initiating monotherapy with lamotrigine, levetiracetam or zonisamide in patients with untreated focal onset seizures.

Arm B - To compare the clinical and cost-effectiveness of initiating monotherapy with levetiracetam or valproate in patients with untreated generalised onset seizures or untreated seizures that are difficult to classify.

Arm A & B

- Compare QOL outcomes of initiating standard or new AEDs
- Examine the development and evolution of QOL impairments in patients with newly treated epilepsy

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

2.5 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 leaflet.

2.5.1 Potential Risks

The main risk of SANAD-II is that patients may be allocated to a treatment that on final analysis is found to be less effective than or have a higher adverse event rate than another, but there is currently clinical equipoise among the treatments being tested. However, treatment will be modified if a decision is made by the prescribing physician and patient that seizure control is inadequate or adverse events are unacceptable. For women of childbearing age, the precise teratogenic risks associated with levetiracetam or zonisamide are unknown and this will be clearly outlined in the patient information leaflet.

2.5.2 Known Potential Benefits

The potential benefits are outlined in section 2.33

Patients recruited into SANAD-II will receive standard NHS care during the conduct of the trial. The main potential benefit is that patients might receive treatment with a new drug which is either more effective and/or better tolerated than the standard treatment.

3 SELECTION OF CENTRES/CLINICIANS

Centres meeting the following criteria will be selected for the trial. The SANAD-II trial will take place in NHS out-patient epilepsy, general neurology and paediatric (epilepsy and general) clinics in the UK. The study will be coordinated through the UK Epilepsy Research Network, the Medicines for Children Research Network, the Wales Epilepsy Research Network and the Comprehensive Clinical Research Network (CCRN).

Study centres will be initiated once all global (e.g. Ethics approval, local R&D approval) and study-specific conditions (e.g. training requirements) have been met, and all necessary documents have been returned to the coordinating centre. Initiation meetings will cover the requirements outlined in CTRC SOPs TM017 and TM018.

3.1 Centre/Clinician Inclusion Criteria

a. Experienced in treating epilepsy
b. Local R&D approval
c. Completion and return of 'Signature and Delegation Log' to the coordinating centre
d. Signed contract between centre and sponsor
e. Receipt of evidence of completion of (b), (c) and (d) by the coordinating centre

3.2 Centre/Clinician Exclusion Criteria

a. Not meeting the inclusion criteria listed above

4 TRIAL OUTCOMES

4.1 Primary Outcome

Time to 12 month remission from seizures

4.2 Secondary Outcome(s)

a. Time to treatment failure
b. Time to treatment failure due to inadequate seizure control. This event will have occurred when the clinician and/or patient decide that treatment replacement or 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.
c. Time to treatment failure due to unacceptable adverse events. This event will have occurred when the patient experiences adverse events attributed to the drug necessitating its withdrawal.
d. Time to first seizure
e. Time to 24 month remission
f. Adverse Reactions
g. QOL
h. Health economic outcomes expressed as the incremental cost per quality-adjusted life-year (QALY) gained

5 STUDY POPULATION

5.1 Inclusion Criteria

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

a. Aged 5 years or older
b. Two or more spontaneous seizures that require antiepileptic drug treatment
c. Untreated and not previously treated with antiepileptic drugs, except emergency treatment in the past 2 weeks
d. Antiepileptic drug monotherapy considered the most appropriate option
e. Willing to provide consent (patients parent/legal representative willing to give consent where the patient is aged under 16 years of age or is lacking capacity to consent)

5.2 Exclusion Criteria

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

a. Provoked seizures only (e.g. alcohol or drug-induced)
b. Acute symptomatic seizures only (e.g. within 1 month from acute brain haemorrhage or brain injury or stroke)
c. Currently treated with antiepileptic drugs
d. Progressive neurological disease (e.g. known brain tumour)

5.3 Patient Transfer and Withdrawal

In consenting to the trial, patients are consented to trial treatment, follow-up and data collection.

5.3.1 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 or for follow-up via GP.

A copy of the participant's case report forms (CRFs) should be provided to 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. The coordinating centre should be notified in writing of patient transfers.

5.3.2 Withdrawal from randomised drug

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.

5.3.3 Withdrawal from Trial Completely

Patients (or patients parent/legal representative where the patient is aged under 16 years of age or is lacking capacity to consent) are free to withdraw consent at any time without

providing a reason. Patients who wish to withdraw consent for 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 and the coordinating centre should be informed in writing by the responsible physician and a withdrawal CRF should be completed to capture the date and reason for trial withdrawal. 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 spontaneous seizures that require antiepileptic drug treatment and have not previously been treated with antiepileptic drugs will be screened at the study centres to identify potentially eligible participants for the study. SANAD II is a pragmatic trial recruiting incident cases and prospective "screening log" will not be maintained.

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).

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 use the baseline CRF to collect 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. 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 DNA sample is provided DNA sample CRF need to be completed. Once all eligibility criteria have been assessed, full eligibility must be confirmed. Full eligibility may only be confirmed by a doctor who has been authorised to do so on the site Delegation Log; a record of this confirmation must be made in the patient's medical notes. 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) Written consent has been obtained from the patient (Parent/legal representative where the patient is under 16 years of age or is lacking capacity to consent)
b) The baseline CRF has been completed
c) Full eligibility has been confirmed by a doctor

The arm (A or B) to which the patient is assigned will be decided by the recruiting physician based upon their epilepsy classification. Patients will then be randomised to one of the following treatments:

Arm A: lamotrigine, levetiracetam or zonisamide (in a 1:1:1 ratio)
OR
Arm B: levetiracetam or valproate (in a 1:1 ratio)

Participants will be randomised using a secure (24-hour) web based randomisation programme controlled centrally by the Clinical Trials Research Centre (CTRC). Personal login username and password, provided by the CTRC, will be required to access the web-based randomisation system. When eligibility has been confirmed each participant will be allocated a unique study number (randomisation number), which will be the primary identifier for all the participants in the study. Treatment allocation will be displayed to the authorised randomiser on a secure webpage and an automated email confirmation will be sent to the authorised randomiser, PI and the trial coordinator.

Randomisation:
Web access https://mcrnctu.org.uk/SANAD2/Home/Login

If there are any problems with the randomisation systems or in case of a randomisation system failure contact

the coordinating centre on 0151 529 5464 / 5463 or via email on sanad2@liv.ac.uk
or
the CTRC helpdesk on 0845 68 00 951 or via email on helpdesk@mcrnctu.org.uk

(Note that the CTRC and the coordinating centre are open from 0900 – 1700, Monday – Friday, excluding public holidays)

In the event of a randomisation system failure, the centre should contact immediately the coordinating centre or the CTRC (Monday to Friday between 9:00 to 17:00 excluding bank holidays) to try to resolve the problem. If the problem can't be resolved the central coordinating centre will perform central randomisation and randomise the participant using the back-up randomisation system. The back-up randomisation system is an exact replica of the live system but is based on a standalone pc at CTU.

Research staff will be trained to use the randomisation system, following this they will be issued with usernames and passwords.

7 TRIAL TREATMENTS

7.1 Introduction

SANAD-II is essentially two randomised controlled trials run in parallel. Patients with untreated focal onset seizures will enter Arm A and will be randomised to treatment with lamotrigine, levetiracetam or zonisamide. Patients with untreated generalised onset seizures or untreated seizures that are difficult to classify will enter Arm B and will be randomised to treatment with levetiracetam or valproate.

Randomised treatment should begin within 7 days of randomisation. The research team should ensure that the duration between obtaining consent, performing baseline assessments, randomisation and the start of 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 section 6 and 8.

All treatments will be prescribed and issued as per routine NHS practice.

Patients will be accrued over a 3.5 year period (4.5 year period for Arm A) and follow up will continue for a further two years. Thus the maximum time that a patient will receive their randomised treatment is 5.5 years (about 6.5 years in Arm A).

7.2 Formulation, Packaging, Labelling, Storage and Stability

SANAD-II is a pragmatic trial that uses market authorised drugs within the terms of marketing authorisation. Based on the marketing authorisation status of the medicines being investigated SANAD-II trial is categorised as ***Type A*** *with* ***"no higher than the risk of standard medical care"*** (see section 13.1)(25). All treatments will be taken as formulations already licensed to be used in UK. There will be no modifications made to the products or their outer packaging, therefore the annex 13 requirements do not apply and 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 PI 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 SPCs provided as separate documents to this protocol.

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 in section 7.3.1 and section 7.3.2, 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.

7.3.1 Arm A – Titration and Initial Maintenance Dose

Table 1: Arm A. Age > 12 years: Titration and Initial Maintenance Dose

Lamotrigine	**Levetiracetam**	**Zonisamide**
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*	250mg once per day for 2 weeks 250mg twice per day for 2 weeks 250mg morning and 500mg night for 2 weeks 500mg twice per day - *initial target maintenance dose*	50mg once per day 2 weeks 50mg twice per day for 2 weeks 50mg am 100mg pm for 2 weeks 100mg am 100mg pm - *initial target maintenance dose*

Table 2: Arm A. Children aged 5-12 years: Titration and Initial Maintenance Dose

Lamotrigine	**Levetiracetam**	**Zonisamide**
0.5 mg/kg/ day as a once a day dose for 2 weeks 0.5 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*	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*	0.5 - 1 mg/kg/day as a once or twice daily regimen (depending on the child's weight) for 2 weeks 1 - 1.5 (maximum) mg/kg/day as a twice daily regimen for 2 weeks 2 - 2.5 (maximum) mg/kg/day as a twice daily regimen for 2 weeks 3 - 4 mg/kg/day as a twice daily regimen for 2 weeks 5 mg/kg/day as a twice daily regimen - *initial target maintenance dose*.

7.3.2 Arm B - Titration and Initial Maintenance Dose

Table 3: Arm B. Age > 12 years: Titration and Initial Maintenance Dose

Valproate	**Levetiracetam**
500mg once per day for 2 weeks 500mg twice per day - *Initial target maintenance dose*	250mg once per day for 2 weeks 250mg twice per day for 2 weeks 250mg morning and 500mg night for 2 weeks 500mg twice per day - *initial target maintenance dose*

Table 4: Arm B. Children aged 5-12 years: Titration and Initial Maintenance Dose

Valproate	**Levetiracetam**
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*	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*

7.4 Unblinding

SANAD-II is an open trial therefore unblinding is not required.

7.5 Accountability and Assessment of Compliance with Study Treatments

SANAD II is a pragmatic rather than exploratory trial and the intention is to measure outcomes associated with treatment policies, which reflect real life clinical practice in the NHS. There are no formal accountability measures required for the trial, as treatments will be prescribed according to the local medical practices and dispensed by hospital and community pharmacies as they would be normally 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 asked about adherence in the QOL questionnaires to allow a description of the policy, but no formal measurements of plasma drug levels are planned nor will the primary analyses be adjusted for actual or estimated adherence.

7.6 Concomitant Medications/Treatments

SANAD-II is an unblinded trial 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 (dose increased or reduced) if further seizures or adverse events occur as is usual clinical practice. The decision to change or discontinue allocated trial treatment is at the discretion of the treating physician and patient. Treatment may be changed or discontinued at any point during the trial period for reasons such as inadequate seizure control, unacceptable adverse events, any change in the participant's condition that the physician believes warrants a change in medication. Any changes in medication must be documented on the appropriate follow up CRF along with the justification for those changes. If a participant's treatment stops prematurely, the reason for discontinuation should be recorded on the appropriate follow up CRF 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 epilepsy trials. Where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the SANAD-II trial this must first be discussed with the coordinating centre who will contact the Chief Investigator (Professor Tony Marson).

8 ASSESSMENTS AND PROCEDURES

Data collection will use paper CRFs and participant completed questionnaires (see section 13. 3 for details on the data capture methods).

Participating centres will be expected to each maintain a file of essential trial documentation (Site File), which will be provided by the coordinating centre, and keep copies of all completed CRFs.

All paper CRFs (except for GP CRF) should be completed as described in section 13.3 by personnel named on the delegation log as authorised to do so, usually the RN, photocopied and originals returned to the coordinating centre within 7 days of the time specified for completion, unless stated otherwise. The GP CRF will be completed at the GP surgery by the patient's GP or a delegate, as per local policy.

Once written informed consent has been obtained from the patient, parent or legally acceptable representative, the research team will collect baseline characteristics using the baseline CRF and the patient will be randomised and followed-up in the trial. For screening and randomisation procedures refer to section 6. For details of procedures associated with trial treatments refer to section 7. For a summary of trial assessments see Table 5 in section 8.1.

Participant details including name, initials, date of birth and randomisation number will be reported on the consent form, separate to clinical data. Participant contact details including name, address and telephone number will be reported on the contact details CRF, separate to clinical data.

8.1 Schedule for Follow-up

The expected duration of follow-up for each participant is between a minimum of 2 years and a maximum of 6.5 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 who will be the main prescribers of AEDs in this trial.

Patients will be followed up as per routine clinical practice and typically at 3, 6, and 12 months and annually thereafter. Patients will be seen at other times as clinically indicated. In these instances, the delegated member of the research team should complete the Follow up Visit CRF.

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 Withdrawal CRF will be completed to capture the date and reason for trial withdrawal as detailed in section 5.3.2.

Table 5: Trial Assessments

Procedures		Baseline (T0)[1]	Follow Up Schedule: T0+3 months	Follow Up Schedule: T0+6 months	Follow Up Schedule: T0+12 months and annually thereafter
Signed Consent Form		X			
Assessment of Eligibility Criteria		X			
Contact details		X			
Review of Medical History including: • Seizure history • Neurological insult • Febrile seizures • Family history of epilepsy • EEG results • Imaging results (CT or MRI)		X			
Further investigation (EEG / CT/ MRI)		(X)			
Allocation of Study Treatment		X			
Issue of Questionnaires[2] in person[3] or by post[4]		X	X	X	X
Review of seizure occurrence & hospital admissions			X	X	X
Review of Anti Epileptic Drug Use (Study Treatment & Concomitant): • Since last follow up • Changes made to treatment plan including reasons			X	X	X
Assessment of Adverse Events			(X)	(X)	(X)
Resource use			X	X	X
Re-Issue of Questionnaire[2] by post[4] or at site[3] to non-responders typically three weeks later		(X)	(X)	(X)	(X)
Telephone follow up of questionnaire non-responders typically three weeks later		(X)	(X)	(X)	(X)
Special Assay or Procedure[5]	Consent and obtain saliva or blood sample for later DNA analysis	(X)			

(X) – As indicated/appropriate.

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

2 Refer to section 8.4 for specification of questionnaire types

3 Questionnaire issued by the research team at site at baseline and routine clinic appointments and posted back to coordinating centre

4 Questionnaire posted to the participant by the coordinating centre and posted back to the coordinating centre

5 See section 8.6

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 CRF, providing a subjective measure of efficacy.

8.2.2 Quality of Life & Utility Scores

The Quality of Life (QoL) (Section 8.4) and Resources Use (Section 8.5) obtained throughout the trial can be used as a subjective measure of efficacy.

8.3 Procedures for Assessing Safety

An assessment of adverse events will be undertaken at each study visit. These reviews should be carried out by the PI or delegated research staff. Adverse event reporting is detailed fully in Section 10.

8.4 Quality of Life and Utility Assessments

For adults, QOL outcomes will be assessed using subscales (adverse drug effects, anxiety/depression, seizure worry, mastery, stigma and overall QOL) of the NEWQOL battery and the Impact of Epilepsy Scale (26). For children and adolescents aged under 16 years, QOL assessment will involve both patient and parent-based measures: children aged 8-15 years and 11 months will complete a generic health status measure validated for use in epilepsy, the KINDL (measures physical, social, emotional, self-esteem, family and school QOL domains) (27); and the 'epilepsy impact' and 'attitude to epilepsy' subscales of the QOLIE-AD (28). Parents of all children will also complete proxy QOL questionnaires (see Table 6 below).

Utility scores will be elicited directly from trial participants (or indirectly via the parents or guardians of children). Adult and adolescent patients will be asked to complete the EQ-5D questionnaire and Visual Analogue Scale. Although the EQ-5D-3L has been used previously in paediatric populations, although it has not been formally validated for use in children (29), and EQ-5D-3L weights are validated for adults aged ≥18 years. The currently recommended approach of using parental proxy reports of (health-related) quality of life for this age group will be used (30). EQ-5D-3L-Y (youth version) will additionally be administered to children aged 8-15 years. All trial participants will be asked to complete an epilepsy-specific utility measure, based on the NEWQOL-6D questionnaire (31).

For ease of administration the required questionnaires have been combined into age appropriate booklets as detailed in Table 6.

The questionnaires to be completed at baseline will be provided to the participant and/or parent as applicable on the day of randomisation by the research team. Participants and/or their parent will be asked to complete the questionnaires at home or in clinic, if they need

help, and return them by post to the coordinating centre using the pre-paid envelope provided. If needed the coordinating centre will re-send the baseline questionnaires three weeks later.

As the timing of out-patients appointments following randomisation will vary according to clinical need and local service delivery, follow-up questionnaires will be posted to the participant or their parent by the coordinating centre at pre-specified time-points. The coordinating centre will contact non-responders by telephone typically three weeks later. Follow on from this telephone contact, if needed, the coordinating centre will re-send the questionnaires.

If the timing of out-patient appointments does not coincide with the pre-specified time-points for questionnaires completion, patients will be provided with follow-up questionnaires by the research team at site when they attend. To facilitate this the coordinating centre will provide questionnaire booklets to sites.

Table 6: Age-appropriate Questionnaires Booklets

Participant Age	Questionnaire Booklet Completed By:	
	Participant	Parent/Carer
5 - 7	-	Kiddy-KINDL EQ-5D-3L & EQ-VAS NEWQOL-6D
8 - 11 (Children)	Kid-KINDL EQ-5D-3L-Y & EQ-VAS QOLIE-AD	Kid-KINDL EQ-5D-3L & EQ-VAS NEWQOL-6D
12 - 15 (Young people)	Kiddo-KINDL EQ-5D-3L-Y & EQ-VAS QOLIE-AD	Kiddo-KINDL EQ-5D-3L & EQ-VAS NEWQOL-6D
≥ 16 (Adult)	Impact of Epilepsy Scale EQ-5D-3L & EQ-VAS NEWQOL-6D	-

8.5 Resources Use and Cost Data

For the health economic assessment, direct costs of health care resources used by patients in the trial will be collected in three ways:

i. A modified version of the Client Service Receipt Inventory (CSRI) (32) will be used to assess patients' use of primary and community care services and personal social services (e.g. primary care services (including out of hours services), NHS Direct, Walk-in treatment centres, and home visits etc.).

ii. Patients' use of secondary care services will be accessed as Hospital Episode Statistics (HES) data via the NHS Digital. Downloaded Healthcare Resource Group (HRG) data will include information on out-patient epilepsy, general neurology and paediatric clinics visits; accident and emergency attendance, and length (and nature) of hospitalisations.

iii. Resources triggered by adverse events will be captured in the follow-up CRF for each patient experiencing an adverse event requiring hospitalisation. Because of potential issues related to completeness of routine data, these will be used to compliment HES data.

Unit costs will be taken from the NHS reference costs database (33); and other appropriate sources (34, 35).

8.6 Sub-studies

8.6.1 Genetic Study

DNA will be collected from every patient randomised in SANAD-II, subject to appropriate consent. This will build on our established Wellcome Trust funded DNA bank of epilepsy patients recruited in SANAD-I (n=1,000 collected DNA samples).

Identification of genetic factors associated with response to treatment in epilepsy is important and may ultimately help to optimise efficacy, tolerability and safety of antiepileptic drugs. To date, the majority of studies assessing genetic contributions to treatment outcome in epilepsy have used retrospective case control designs, which have been confounded by problems such as the retrospective definition of outcomes, a lack of consistency in phenotyping approaches, and an inability to account for environmental factors. This has often resulted in findings that have not been replicated.

The collection of DNA from approximately 1,500 newly-treated epilepsy patients in SANAD II, and whose clinical outcomes have been validated within a prospective trial, will establish an unrivalled resource for the identification of genetic and clinical factors, and their interactions, that contribute to therapeutic success or failure and thereby inform optimal drug choice for the individual. The strength of our preferred, prospective pharmacogenetic approach has already been demonstrated in SANAD-I (36) and was applauded by commentators (37).

Our group currently holds the world's largest collection of DNA and prospectively accrued outcome data from newly-treated epilepsy patients and which is contributing to the work-plan of the NHS Chair in Pharmacogenetics and to worldwide consortia being established through the International League Against Epilepsy. If understanding of the genetic contributions to treatment outcome in epilepsy is to be improved, it is essential that DNA is collected in conjunction with all prospective epilepsy trials, such as SANAD-II. DNA samples may also contribute as controls in other disease areas.

DNA collection will be included as an option on the SANAD-II consent form in order that refusal will not preclude participation in the trial itself. Samples, preferably in the form of whole venous blood, will typically be collected at baseline (or at a subsequent follow-up visit, as convenient), shipped to the Department of Molecular and Clinical Pharmacology at The University of Liverpool, and extracted and stored in a state-of-the-art DNA archive. Saliva samples will be collected from patients unable to provide a blood sample.

8.7 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 speciality care then follow-up will also be attempted through this latter clinician. Where these attempts are unsuccessful, the participant's GP will be asked to contact the family and provide follow-up information to the recruiting centre. This information will be included on the patient information sheet. Wherever possible, information on the reason for loss to follow-up will be recorded.

8.8 GP follow-up

Where patients default from clinic follow-up, follow-up information will be sought from their GPs. The coordinating centre will ask patient's GP or delegate to complete a paper CRF and to post it back to the coordinating centre.

8.9 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 Data and Safety Monitoring Committee (IDSMC).

9 STATISTICAL CONSIDERATIONS

9.1 Introduction

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

9.2 Method of Randomisation

Randomisation will use a minimisation program with a built in random element utilising factors that will not be made known to individuals in charge of recruitment to minimise any potential for predicting allocation.

9.3 Outcome Measures

See section 4.

9.4 Sample Size

SANAD-II is powered to detect non-inferiority of the new antiepileptic drugs (levetiracetam and zonisamide) compared to standard treatments (lamotrigine or valproate) for the primary outcome time to 12-month remission. A new drug might become a standard first line treatment if it is proven to be non-inferior for efficacy but superior for tolerability when compared to a standard treatment – tolerability is examined in secondary outcomes including time to treatment failure for adverse effects. Powering the study for non-inferiority will also provide sufficient power to detect important differences between treatment policies.

The ILAE Commission on Antiepileptic Drugs defined limits of equivalence of +/- 10% for the primary outcome in antiepileptic drug monotherapy studies (38). However the Commission was not explicit as to whether this should be on the hazard ratio or absolute scale. No empirical work has yet been undertaken to underpin the choice of equivalence or non-inferiority margins in epilepsy trials. The CI has given numerous seminars and lectures in the UK and elsewhere about epilepsy trial methodology and the audience typically vote for a margin of 10% around absolute differences between AEDs for monotherapy studies when given examples of margins ranging from 20% to 5%. Communicating treatment differences to patients on a hazard ratio scale is extremely difficult compared to a discussion of absolute differences at specific time points. Given that the ultimate purpose of SANAD-II is to provide information that patients and clinicians can use to help them make treatment decisions, the NI margin for SANAD-II has been chosen according to absolute differences.

Calculations have been informed by the SANAD-I study which estimated the 12 month remission-free probability (at 24 months) as 0.43 (exponential hazard rate of 0.0352) for lamotrigine (Arm A standard) and 0.31 (exponential hazard rate of 0.0488) for valproate (Arm B standard). The calculations assume a HR of 1.0, 80% power, and allowance for approximately 5% losses to follow-up throughout, as occurred in SANAD-I. For patients with focal-onset seizures (Arm A) two primary comparisons are of interest (levetiracetam vs lamotrigine and zonisamide vs lamotrigine), therefore the one-sided significance level has

been divided by two (one-side alpha 0.0125). Assuming a 10% absolute difference in survival probability, the non-inferiority margin on the hazard ratio (HR) scale is ln(0.43)/ln(0.53)=1.329. After adjusting for 5% losses to follow-up, 330 patients are required in each of 3 treatment groups (990 total for Arm A). For patients with generalised-onset seizures or seizures that are difficult to classify (Arm B) there is only one comparison of interest (levetiracetam vs valproate). Assuming a 10% absolute difference in survival probability, the non-inferiority margin on the HR scale is ln(0.31)/ln(0.41)=1.314 for Arm B. Therefore, with a one-sided alpha of 0.025, 260 patients are required in each of two treatment groups allowing for 5% losses to follow-up (520 total for Arm B). The total number of patients required is 1510.

9.5 Interim Monitoring and Analyses

Formal interim analyses of the accumulating data will be performed at regular intervals (at least annually) for review by an Independent Data Monitoring and Safety Committee (IDSMC). These analyses will be performed at the CTRC. The IDSMC will be asked to give advice on whether the accumulated data from the trial, together with results from other relevant trials, justifies continuing recruitment of further patients or further follow-up. A decision to discontinue recruitment, in all patients or in selected subgroups will be made only if the result is likely to convince a broad range of clinicians including participants in the trial and the general clinical community. If a decision is made to continue, the IDSMC will advise on the frequency of future reviews of the data on the basis of accrual and event rates. The IDSMC will make recommendations to the Trial Steering Committee (TSC, see section 16) as to the continuation of the trial.

9.6 Analysis Plan

All primary analyses will be on an intention to treat (ITT) basis including all randomised patients retained in their randomised treatment groups. Separate analyses will be undertaken for each randomisation arm (Arm A = lamotrigine vs levetiracetam, and lamotrigine vs zonisamide; Arm B = valproate versus levetiracetam). The interval (in days) from randomisation to occurrence of a 12 month remission will be summarised by Kaplan-Meier curves for each treatment group. Survival regression models will be explored; two different models will be used: (i) including the treatment effect only using treatment indicator variables; (ii) including the treatment effect together with covariates. The impact of centre effect on the treatment comparison will be investigated by considering both fixed and random effect models. When analyzing the data using the fixed effect approach, the centre effect is to be modelled by a series of dummy variables. However due to concern regarding the number of dummy variables required, a random effect analysis will also be considered. A per protocol analysis will be undertaken to assess the robustness of ITT analyses. Sensitivity analyses will be carried out to assess the robustness of conclusions under (a) different imputation rules for missing data, and (b) if misdiagnoses are excluded. For Trial Arm B, an additional analysis of the primary outcome will add a stratification variable to the model: seizure type (generalised / unclassified).

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 Haybittle-Peto approach will be employed for each interim analysis, with 99.9% confidence intervals calculated for interim analysis effect estimates. The final analysis will be undertaken at the end of the trial when all patients have a minimum two year follow-up data (five and a half years after the first patient is randomised) and 95% confidence intervals will be calculated.

For each arm, each population (child/adult/parent-carer), and for each outcome applicable within that population QOL data will be analysed longitudinally using repeated measures random effects modelling to explore between treatments changes in scale scores over time, taking account of baseline QOL..

For the analysis of adverse reactions, all patients who received any amount of each study drug will be included in the safety analysis dataset in the treatment group they actually received. All adverse reactions and serious adverse reactions reported by the clinical investigators will be presented, identified by treatment group. Adverse reactions (ARs) will be grouped according to a pre-specified coding system and tabulated. The number (and percentage) of patients experiencing each AR, and the number (and percentage) of occurrences of each AR will be presented. No formal statistical testing will be undertaken.

9.7 Health Economic Evaluation

For the health economic analyses, the perspective of the NHS and Personal Social Services will be adopted for costing purposes. It will be assessed whether levetiracetam or zonisamide as monotherapy in newly-treated focal epilepsy are cost-effective by estimating the incremental cost-utility and cost-effectiveness ratios relative to lamotrigine and to each other. The same approach will be used to compare levetiracetam and valproate for generalised-onset seizures. A cost consequence analysis (40) will be conducted to consider non-health benefits which are neither captured within the QALY calculation, nor in the cost-effectiveness analyses. Potential non-health benefits that will be measured include: social activity, time in work or school and patients' driving (captured in the NEWQOL battery). Additional non-health benefits (perceived stigma, control, and cognitive effects) will also be captured in the NEWQOL-6D (31).

Sensitivity analyses will be conducted to test the robustness of our findings. These analyses will be based on the observed distributions of outcome and costs to test whether, and to what extent, the incremental cost-utility and cost-effectiveness ratios are sensitive to key assumptions in the analysis. Uncertainty in parameter estimates will be addressed through the application of bootstrapping and the estimation of cost-effectiveness acceptability curves.

The estimated incremental cost per QALY, per seizure avoided and per 12 month remission will be compared with the results of other economic assessments of antiepileptic drugs (41, 42).

10 PHARMACOVIGILANCE

10.1 Terms 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 an SAE.
***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.

Suspected Unexpected Serious Adverse Reaction (SUSAR)
An adverse reaction that is classed in nature as serious and which is not consistent with the information about the medicinal product in question set out:

in the case of a licensed product, in the summary of product characteristics for that product; in the case of any other investigational medicinal product, in the IB relating to the trial in question.

10.2 Notes Severity / Grading of Adverse Events

The assignment of the severity/grading should be made by the investigator responsible for the care of the participant using the definitions below.
Regardless of the classification of an AE as serious or not, its severity must be assessed according to medical criteria alone using the following categories:

Mild: does not interfere with routine activities
Moderate: interferes with routine activities
Severe: impossible to perform routine activities

A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 10.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

10.3 Relationship to Trial Treatment

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in Table 7.

If any doubt about the causality exists the local investigator should inform the study coordination centre who will notify the Chief Investigator. In the case of discrepant views on causality between the investigator and others, the MHRA will be informed of both points of view.

Table 7: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. There is an alternative cause for the AE.
Unlikely	There is little evidence to suggest there is a causal relationship (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 condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. 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 event (e.g. the participant's clinical condition, other concomitant treatments).
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.

For the purpose of pharmacovigilance reporting in SANADII, an AE whose causal relationship to the randomised study drug or other anti-epileptic drug assessed by the investigator as "possible", "probable", or "almost certainly" is classed as an Adverse Reaction (AR) and is reportable for SANADII (see section 10.5).

10.4 Expectedness

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

All events judged by the designated investigator to be possibly, probably, or almost certainly related to the IMP and graded as serious will be assessed for expectedness by the Chief Investigator (or designated other specified in the protocol). If latter judged as **unexpected** (i.e. not listed in the relevant SPC) should be reported as a SUSAR.

10.5 Reporting Procedures

AEs will only be reported where the causal relationship to the trial treatment or other anti-epileptic treatment has been assessed and judged by the investigator to be possibly, probably or almost certainly related the trial treatment or other anti-epileptic treatment (see section10.3), which occurs from the time of consent until the final follow-up visit. 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.

10.5.1 Events to be Reported Include

Include the following only if they are possibly, probably or almost certainly related the trial treatment or other anti-epileptic treatment:

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition
- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment
- Laboratory abnormalities that require clinical intervention or further investigation (unless they are associated with an already reported clinical event).
- Abnormalities in physiological testing or physical examination that require further investigation or clinical intervention
- Injury or accidents

10.5.2 Events to be Reported Do Not Include

I. Any AE whose causal relationship to the trial treatment or other anti-epileptic treatment is assessed and judged by the investigator to be unrelated or unlikely to be related to the trial treatment or other antiepileptic treatment

- Any SAE whose causal relationship to the trial treatment or other anti-epileptic treatment is assessed and judged by the investigator to be unrelated or unlikely to be related to the trial treatment or other antiepileptic treatment unless it is a pregnancy, death or hospital admission. Reporting procedures for these SAEs are described in sections 10.5.5, 10.5.6 and 10.5.7.
- 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

10.5.3 Non serious ARs

All such reactions, whether expected or not, should be recorded on an Adverse Reaction Form, which should be transmitted to the coordinating centre within seven days of the form being updated.

10.5.4 Serious ARs/SUSARs

- **Trial AEDs**

SARs and SUSARs to any of trial AEDs (lamotrigine, levetiracetam, zonisamide and valproate) even if not the randomised treatment) should be reported within 24 hours of the local site becoming aware of the event. All reported SARs associated with trial AEDs will be assessed for expectedness by the Chief Investigator (or designated other specified in the protocol) and if judged as unexpected will be reported by the coordinating centre as SUSARs (see section 10.4).

The SAR form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator should assign the causality of the event. Additional information should be sent within 5 days if the reaction has not resolved at the time of reporting.

The coordinating centre will notify the MHRA, main REC and IDSMC of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study. Local investigators should report any SUSARs and /or SARs as required locally.

SARs and SUSARs to trial AEDs must be reported by faxing a completed SAR CRF within 24 hours of the local site becoming aware of the event to the coordinating centre
Fax: 00 44 (0) 151 529 5466
(see section10.7 for further details)

- **Non-trial AEDs**

SARs associated with any other antiepileptic treatment (not a trial AEDs) will be reported to the coordinating centre on AR CRF form as per routine schedule. Any further reporting would be per local policy.

SARs to non-trial AEDs must be reported to the coordinating centre on AR CRF form as per routine schedule

10.5.5 Reporting of Pregnancy

Any pregnancy which occurs during the study should be reported to the coordinating centre using a pregnancy CRF within 24 hours of the site becoming aware of its occurrence. All pregnancies that occur during treatment need to be followed up until after the outcome using the pregnancy CRF. Any SAR or SUSAR experienced during pregnancy must be reported on the AR or SAR form as appropriate (see section 10.5.4).

The investigator should contact the participant to discuss the risks of continuing with the pregnancy and the possible effect to the foetus. Appropriate Obstetric care should be arranged.

The coordinating centre will report all pregnancies to the trial co-sponsors every 6 months.

Pregnancies must be reported by faxing a completed Pregnancy CRF within 24 hours of the local site becoming aware of the event to the coordinating centre
Fax: 00 44 (0) 151 529 5466

10.5.6 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 death CRF **within 7 days** of the clinical research team becoming aware of the event. If a patient's death has been assessed and judged by the investigator to be possibly, probably or almost certainly related to any of the trial treatments (see section 10.3) should be reported as described in section 10.5.4.

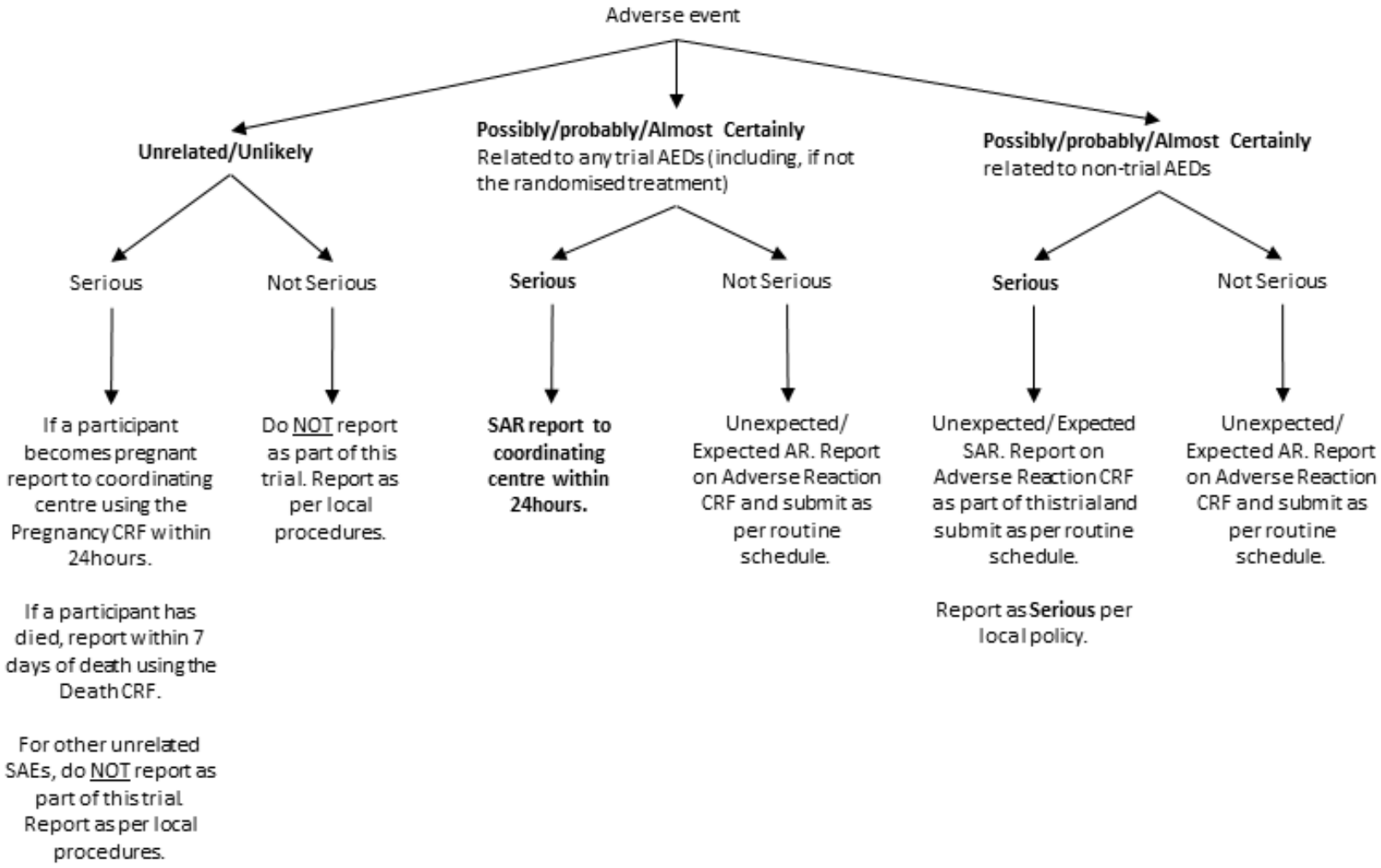
10.5.7 Reporting of Hospital Admissions

Information about **hospital admissions** will be collected through HES. Any hospital admissions fulfilling the criteria of a SAR or SUSAR should be reported as described in section 10.5.4.

10.6 Follow-up After Adverse Reactions

All adverse reactions 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 ARs, 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.



Flowchart for determining of reporting requirements.

10.7 Responsibilities – Investigator

The Investigator is responsible for reporting all ARs and SARs that are observed during the study and fulfil the criteria listed in Section 10.5.

- All ARs should be reported on the AR CRF and returned to the coordinating centre as per routine schedule.
- All SARs to any of the trial AEDs (including when not the randomised treatment) must be reported immediately by the investigator to the coordinating centre on an SAR form.
- SARs to any other anti-epileptic treatment (non-trial AEDs) should be reported on the AR CRF as part of this trial and CRF form returned to the coordinating centre as per routine schedule.

All pregnancies, deaths or hospital admissions should be reported as described in sections 10.5.5, 10.5.6 and 10.5.7.

Minimum information required for SAR reporting:

- Study identifier
- Study centre
- Patient number
- Date of randomisation
- 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
- SAR outcome

i. The SAR form should be completed by a designated investigator, a physician named on the 'signature list and delegation of responsibilities log' as responsible for reporting SARs and making trial related medical decisions. The investigator should assess the SAE for the likelihood that it is a response to the investigational medicinal product or other anti-epileptic drug. In the absence of the designated investigator the form should be completed and signed by an alternative member of the research site trial team and submitted to the coordinating centre. As soon as possible thereafter the responsible investigator should check the SAR form, make amendments as appropriate, sign and re-send to the coordinating centre. The initial report shall be followed by detailed reports as appropriate.

ii. When submitting a SAR form to the coordinating centre research sites should also telephone the appropriate trial co-ordinator/data manager on

Telephone number 0151 529 5464

to advise that an SAR report has been submitted. (The coordinating centre trial team should ensure that the number to be used to report SARs in this way is manned during office hours, and is notified to research site personnel during the site initiation process.)

iii. Send the SAR form by fax (within 24 hours) to the coordinating centre:

Fax Number: 0151 529 5466

iv. The responsible investigator must **notify** their R&D department of the event (as per standard local governance procedures).
v. In the case of an SAR the participant must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.
vi. Follow-up information is noted on another SAR form by ticking the box marked 'follow-up' and faxing to the coordinating centre as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.
vii. The patient **must** be identified by trial number, date of birth and initials only. The patient's name **should not** be used on any correspondence.

10.8 Responsibilities – CTRC c/o LERG coordinating centre

The LERG coordinating centre as part of the CTRC is undertaking duties delegated by the trial co-sponsors, The Walton Centre Foundation Trust and University of Liverpool, and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA, competent authorities of other European member states in which the trial is taking place and, if required, the research ethics committees) as follows:

- SUSARs which are fatal or life-threatening must be reported not later than 7 days after the coordinating centre is first aware of the reaction. Any additional relevant information must be reported within a further 8 days.
- SUSARs that are not fatal or life-threatening must be reported within 15 days of the coordinating centre first becoming aware of the reaction.
- A list of all SARs (expected and unexpected) must be reported annually.

It is recommended that the following safety issues should also be reported in an expedited fashion

- An increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important;
- Post-study SUSARs that occur after the patient has completed a clinical trial and are notified by the investigator to the sponsor;
- New events related to the conduct of the trial or the development of the IMPs and likely to affect the safety of the subjects, such as:
    a. A serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial;
    b. A significant hazard to the subject population, such as lack of efficacy of an IMP used for the treatment of a life-threatening disease;
    c. A major safety finding from a newly completed animal study (such as carcinogenicity).

d. Any anticipated end or temporary halt of a trial for safety reasons and conducted with the same IMP in another country by the same sponsor;

- Recommendations of the Data Monitoring Committee, if any, where relevant for the safety of the subjects.

Staff at the coordinating centre will liaise with the Chief Investigator (or designated other specified in the protocol) who will evaluate all SARs received for seriousness, expectedness and causality, and those that are identified as SUSARs reported to regulatory authorities and MREC. The causality assessment given by the Local Investigator at the hospital cannot be overruled and in the case of disagreement, both opinions will be provided with the report.

Patient safety incidents that take place in the course of research should be reported to the NHS Commissioning Board Special Health Authority by each participating NHS Trust in accordance with local reporting procedures.

10.8.1 Safety reports

Safety reports will be generated during the course of the trial which allows for monitoring of AR reporting rates across sites. The coordinating centre will send Developmental Safety Update Reports containing a list of all SARs to regulatory authorities and MREC. Any concerns raised by the IDSMC or inconsistencies noted at a given site may prompt additional training at sites, with the potential for the coordinating centre to carry out site visits if there is suspicion of unreported ARs in patient case notes. Additional training will also be provided if unacceptable delay in safety reporting timelines.

11 ETHICAL CONSIDERATIONS

11.1 Ethical Considerations

The study will abide by the principles of the World Medical Association Declaration of Helsinki (1964) and the Tokyo (1975), Venice (1983), Hong Kong (1989) and South Africa (1996).

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.

Informed consent in incapacitated adults: In adults lacking capacity to consent, a personal (or professional) legal representative will be approached to discuss trial participation. The personal (or professional) legal representative will be informed about the trial, the potential risks and benefits associated with the trial participation and their right to withdraw from the trial at any time without being subject to any resulting detriment. They will be provided with written information and contact details of the trial personnel, who will also be readily available, and from whom further information about the trial may be obtained.

DNA sampling: The samples will be labelled with the participant's trial identifier number. The purpose of undertaking genetic testing at some point in the future will be to determine whether those patients with specific polymorphisms differ in their response to particular treatments or whether specific polymorphisms affect severity or long term prognosis of epilepsy. The genetic study will be subject to consent, additional to the main study, and participants who refuse to take part will not be precluded from entry into SANAD-II. The DNA collected will be used for genetic studies in epilepsy and other diseases. Information about individual patients will not be available at any time.

11.2 Ethical Approval

The trial protocol has been submitted to an NRES Multi-centre Research Ethics Committee (MREC) but must undergo independent review at the R&D offices at participating sites. The local R&D office should be sent the appropriate site specific information form complete with the necessary authorisation signatures, plus any other documentation requested for review. A copy of local Research & Development (R&D) approval should be forwarded to coordinating centre before the site is initiated and patients recruited.

Consent and/or proxy consent from the parent or legally acceptable representative should be obtained prior to each patient participating in the trial, after a full explanation has been given of the treatment options, including the conventional and generally accepted methods of treatment. Age and stage-of development specific Patient Information and Consent Forms (PISC) should also be implemented and patient assent obtained where appropriate. 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 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 CTRC coordinated 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. Where appropriate, age-and-stage-of-development appropriate 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 and adults with incapacity) 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 and adults with incapacity). 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, should have 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 and adults with incapacity) 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 and adults with incapacity) 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 and adults with incapacity) for their records. The original copy will be filed in the participant's notes and a further copy of the signed consent form will be retained in the investigator site file. One final copy of the consent form should be sent to the coordinating centre within 7 days of randomisation.

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 or adult with incapacity 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.

11.3.1 Assent in minors

If capable, and under appropriate circumstances, minors should be approached to provide assent by a member of the research team with experience with minors. Age-and-state-of-development IEC-approved 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 take where appropriate and documented in the patient notes, however the absence of assent does not exclude the patient provided consent has been obtained from the parent/legal representative.

11.3.2 Consent in incapacitated adults

In incapacitated adults trial participation will be discussed with a personal (or professional) legal representative by a suitably experienced member of the research team who is listed on the delegation log. They will be provided with written information and asked to sign the Patient Representative Consent Form.

For England, Wales and Northern Ireland personal legal representative is someone suitable by virtue of their relationship with the adult and available and willing to do so. For Scottish sites personal legal representative is a welfare guardian, welfare attorney or nearest relative.

11.3.3 Informed Consent for DNA Collection

DNA collection will be included as optional in the main SANAD-II informed consent form and the same process for obtaining informed consent will be followed as described in section 11.3 above. Refusal for DNA collection will not preclude participation in the trial.

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 REGULATORY APPROVAL

This trial fall within the remit of the EU Directive 2001/20/EC, transposed into UK law as the UK Statutory Instrument 2004 No 1031: Medicines for Human Use (Clinical Trials) Regulations 2004 as amended. This trial will be registered with the MHRA and a Clinical Trial Authorisation (CTA) for Notification sought (see section 13).

13 TRIAL MONITORING

Trial monitoring is carried out to ensure that the rights and well-being of human participants are protected during the course of a clinical trial. A risk assessment is performed for each trial coordinated by the coordinating centre to determine the level and type of monitoring required for specific hazards. The nature and extent of monitoring will be specific to the individual trial. Monitoring can take the form of on-site visits or central monitoring. A detailed monitoring plan will be developed to describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted.

13.1 Risk Assessment

A detailed risk assessment is performed for each trial coordinated by the CTRC to determine the level and type of monitoring required for specific hazards. The nature and extent of monitoring will be specific to the individual trial.

In accordance with the CTRC SOP TM005 this trial has undergone a risk assessment, completed in partnership between:

- Representative/s of the Trial Sponsor
- Chief Investigator
- Trial Coordinator and supervising Trial Manager
- Statistical team
- Information Systems team
- CTRC Director

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.

Monitoring of the SANAD-II trial will be informed by the SANAD-II risk assessment and will be conducted as per a detailed monitoring plan, which will describe who will conduct the monitoring, at what frequency monitoring will be done, and what level of detail monitoring will be conducted.

The outcome of the risk assessment is assigned according to the following categories:

- Low risk
- Moderate risk
- High risk

The outcome of the SANAD-II trial specific risk assessment it that SANADII has been judged as a **Low risk** clinical trial. This level of risk has determined the approach to trial monitoring described in this section.

Guidance issued by the MRC, Department of Health and the MHRA on risk-adapted approaches to the management of CTIMPs (25) propose a three level categorisation for the potential risk associated with the IMP, assigned 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'.*

SANAD-II is a pragmatic trial that uses market authorised drugs within the terms of marketing authorisation. Based on this marketing authorisation status of the medicines being investigated SANAD-II trial is 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.

Trial Oversight Committees related to the monitoring of the trial are detailed in section 16.

13.2 Source Documents

Source data*: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH E6, 1.51).*
Source documents*: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH E6, 1.52).*

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

- Medical Records
- Hard copy questionnaires
- Printouts from automated instruments (EEG & Imaging)

Therefore, for data where no prior record exists and which is recorded directly in the CRF, the CRF will be considered the **source document**, unless otherwise indicated by the investigator. All such exemptions should be identified prior to the clinical phase of the trial. In addition to the above, date(s) of conducting informed consent (plus assent where appropriate and if taken) process including date of provision of patient information, randomisation number and the fact that the patient is participating in a clinical trial (including

allocated treatment arm) should be added to the patient's medical record chronologically, i.e. when treatment is allocated to the patient.

13.3 Data Capture Methods

Data capture will be in the form of paper copies that will be returned as an on-going process from each site to the coordinating centre within 7 days of completion.

13.3.1 Case Report Forms

The study CRF is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "ND". If the item is not applicable to the individual case, write "NA". Or if the data item is un-known, write "NK". If a data item has not been recorded on source data then write 'NR'. All entries should be printed legibly. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialled and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

CRFs should be photocopied at site and the originals returned to the coordinating centre within 7 days of the time specified for completion, unless stated otherwise (photocopies of completed CRFs should be kept in the site file).

The final version of the original page(s) should only be sent into coordinating centre when the patient has completed their time in the trial.

13.3.2 Patient Completed Data

The participant initials and randomisation number should be clearly labelled on all documents. For questionnaires administered by the research team the header containing participant randomisation number and initials should also be completed. Questionnaires should be returned by the patient or parent directly to the coordinating centre using prepaid envelope provided. For further details on the administration of the questionnaires refer to section 8.4.

Patient seizure diaries, if completed, will be presented at each follow up visit and data from them will be captured and transcribed to the medical record. Patient seizure diaries should aid the patient in recording their seizure history.

13.4 Data Monitoring at the coordinating centre

Data stored at the coordinating centre 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 query forms will be produced at the coordinating centre from the trial database and sent either electronically or through the post to a named individual (as listed on the site delegation log). Sites will respond to the queries providing an explanation/resolution to the discrepancies and return the data query forms to coordinating centre. The forms will then be filed along with the appropriate CRFs and the

appropriate corrections made on the database. There are a number of monitoring features in place at the coordinating centre to ensure reliability and validity of the trial data, to be detailed in the trial monitoring plan.

13.5 Clinical Site Monitoring

In order to perform their role effectively, the trial coordinator (or monitor) and persons involved in Quality Assurance and Inspection may need direct access to primary data, e.g. patient records, laboratory reports, appointment books, etc. Since this affects the patient's confidentiality, this fact is included on the Information Sheets and Informed Consent Forms.

13.6 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.
CRFs will be labelled with the patient's initials and unique trial 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 will be undertaking activities requiring the transfer of identifiable data:

1. The coordinating centre will be responsible for administering questionnaires to trial participants following discharge from hospital and therefore will be required to receive contact details including name, address and telephone details.
2. Verification that appropriate informed consent is obtained will be enabled by the provision of copies of participant's signed informed consent/assent forms being supplied to the coordinating centre by recruiting centres, which requires that name data will be transferred to the coordinating centre.

This transfer of identifiable data is disclosed in the PISC forms. The coordinating centre will preserve the confidentiality of participants taking part in the study and The University of Liverpool is registered as a Data Controller with the Information Commissioners Office.

13.7 Quality Assurance and Control

QA includes all the planned and systematic actions established to ensure the trial is performed and data generated, documented/recorded and reported in compliance with applicable regulatory requirements. QC includes the operational techniques and activities done within the QA system to verify that the requirements for quality of the trial-related activities are fulfilled. In accordance with the monitoring plan, site visits will be conducted and source verification performed if indicated to be required as a result of central monitoring processes. To this end:

- The research team (as a minimum the Principal Investigator) from each centre will attend site initiation training, arranged by the coordinating centre, which will incorporate elements of trial-specific training necessary to fulfil the requirements of the protocol

- The Trial Coordinator is to verify appropriate approvals are in place prior to initiation of a site and the relevant personnel have attended trial specific training;
- The Trial Coordinator is to check safety reporting rates between centres;
- The Trial Coordinator is to monitor screening, recruitment and drop-out rates between centres;
- The Trial Coordinator is to conduct data entry consistency checks and follow-up data queries;
- Independent oversight of the trial will be provided by the Independent Data and Safety Monitoring Committee and independent members of the Trial Steering Committee.

13.8 Records Retention

The investigator at each investigational site must make arrangements to store the essential trial documents, (as defined in Essential Documents for the Conduct of a Clinical Trial (ICH E6, Guideline for Good Clinical Practice)) including the Investigator Site File until the Clinical Trials Unit informs the investigator that the documents are no longer to be retained, or for a maximum period of 15 years (whichever is soonest).

In addition, the investigator is responsible for archiving of all relevant source documents so that the trial data can be compared against source data after completion of the trial (e.g. in case of inspection from authorities).

The investigator is required to ensure the continued storage of the documents, even if the investigator, for example, leaves the clinic/practice or retires before the end of required storage period. Delegation must be documented in writing.

The coordinating centre undertakes to store originally completed CRFs for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only. The coordinating centre will archive the documents in compliance with ICH GCP utilising the Records Management Service of the University of Liverpool. All electronic CRFs and trial data will be archived onto an appropriate media for long term accessible storage. Hard copies of data will be boxed and transferred to specially renovated, secure, premises where unique reference numbers are applied to enable confidentiality, tracking and retrieval.

14 INDEMNITY

SANAD-II is sponsored by The Walton Centre Foundation Trust and University of Liverpool and co-ordinated by the LERG as part of the CTRC in the University of Liverpool. The Walton Centre Foundation Trust and University of Liverpool do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot offer any indemnity. The University of Liverpool has clinical trials insurance and professional indemnity policies in place to cover its liabilities in regards to any work undertaken by its staff in the course of their employment at the University. As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply. However, in terms of liability, NHS Trust and Non-Trust Hospitals have a duty of care to patients treated, whether or not the patient is taking part in a clinical trial, and they are legally liable for the negligent acts and omission of their employees. Compensation is therefore available in the event of clinical negligence being proven.

Clinical negligence is defined as:
"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process".

15 FINANCIAL ARRANGEMENTS

This study is funded by the Health Technology Assessment Programme (HTA) of the Department of Health.

15.1 Financial Support to Collaborating Sites

Contractual agreements will be in place between sponsor and collaborating sites that will incorporate financial agreements.

15.1.1 Per patient payments

The HTA has provided funding for per patient payments when participants are recruited and also per follow up visit. The exact amounts are detailed in the contract between Sponsor and site.

Also, as the study is funded by the NIHR HTA, it will be automatically adopted onto the NIHR portfolio, which will allow trusts to apply to their comprehensive local research network for service support costs as required.

16 TRIAL COMMITTEES

16.1 Trial Management Group (TMG)

A Trial Management Group (TMG) will be formed comprising the Chief Investigator, other lead investigators (clinical and non-clinical) and members of the CTRC. The TMG will be responsible for the day-to-day running and management of the trial and will meet as a minimum approximately 3 times a year (refer to the TMG terms of reference and trial oversight committee membership document for further detail).

16.2 Trial Steering Committee (TSC)

The Trial Steering Committee will consist of an independent chairperson, independent experts in the field of epilepsy, a biostatistician and a representative of Investigators, Chief Investigator and Lead statistician The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC (refer to the TSC terms of reference and trial oversight committee membership document for further detail).

16.3 Independent Data and Safety Monitoring Committee (IDSMC)

The independent Data and Safety Monitoring Committee (IDSMC) consists of an independent chairperson, plus 2 independent members: one who is an expert in the field of epilepsy, and one who is an expert in medical statistics.

The IDSMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data. The IDSMC will first convene prior to the start of recruitment and will then define frequency of subsequent meetings (at least annually) (refer to the IDSMC charter and trial oversight committee membership document for further detail). Details of the interim analysis and monitoring are provided in section 9.

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

17 PUBLICATION

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 TMG.

The TMG 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 allocated to this trial should be attached to any publications resulting from this trial.

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

18 PROTOCOL AMENDMENTS

18.1 Version 1 (30/Mar/2012)

Original Approved version.

18.2 Version 2.0 (04/01/2013)

Summary of changes to the protocol within Substantial Amendment No.1:

Section	Page number	Description of changes
Contact details	5	Deleted details for Centre for Medical Statistics and Health Evaluation as it is part of CTRC.
Table of contents	7-9	Page numbers updated.
1 & 5.2	11 & 22	Some of the exclusion criteria are clarified.
2.1	14	Added new sub-section Definitions.
6.1	24	Screening section amended.
7.7	28	Dose modifications section amended.
8.4	31	Quality of Life and Utility Assessments section updated.
10	38-47	Pharmacovigilance section updated to reflect the difference in the reporting procedures for trial and non-trial AEDs.
1-20	1-65	Minor formatting throughout.

18.3 Version 3.0 (07/03/2013)

Summary of changes to the protocol with Substantial Amendment No.2:

Section	Page number	Description of changes
Contact details	5	Text deleted. Contact telephone number and e-mail address for the University of Liverpool updated.
Section 7.2	26	Text deleted to allow all licensed drug formulations to be used.
Section 7.3.1	27	Table 1. Initial target maintenance dose for zonisamide amended.

18.4 Version 4 (13/06/2014)

Summary of changes to the protocol with Substantial Amendment No.5:

Section	Page number	Description of changes
1	13	Two inclusion criteria were amended: • Untreated and not previously treated with antiepileptic drugs, except emergency treatment in the past 2 weeks • Willing to provide consent (patients parent/legal representative willing to give consent where the patient is aged under 16 years of age or is lacking capacity to consent)
5.1	24	Two inclusion criteria were amended: c. Untreated and not previously treated with antiepileptic drugs, except emergency treatment in the past 2 weeks e. Willing to provide consent (patients parent/legal representative willing to give consent where the patient is aged under 16 years of age or is lacking capacity to consent)
5.3.2	24	Text was amended to include patients who lack capacity to consent for themselves.
6.3	26	Text was amended to include patients who lack capacity to consent for themselves.
6.3	27	The randomisation table was re-formatted for clarity. The back-up randomisation system was changed from randomisation envelopes to replica of the randomisation system based on a standalone pc at CTU.
7.3.1	29	Table 1: Arm A. Aged > 12 years. A text 'for 2 weeks' was added after *50mg am 100mg pm* in the zonisamide's column. Table 2: Arm A. Children aged 5-12 years. Titration steps and initial maintenance dose for zonisamide were amended.
8.4	35	Table 6. Group names were added in brackets to the age ranges in the column Participant age.
10.6	44	The flowchart was updated to reflect the verbatim description by removing Unexpected/Expected step, as it is done centrally by the chief investigator.
11.1	48	A paragraph was added regarding the Informed consent in incapacitated adults.
11.3	49-50	Minor amendments to the text.
11.3.3	50	A new section was created to explain the informed consent process in incapacitated adults.

18.5 Version 5 (22/07/2015)

Summary of changes to protocol with Substantial Amendment No.7:

Section	Page Number	Description of changes
Title page	1	NIHR logo updated and funding statement added
Protocol Approval	2	Lead trial statistician's contact details added
Protocol Approval	2	Walton Centre's contact details updated
Contact Details Institutions	5	Walton Centre's contact details updated
Contact details: Individuals	6	Walton Centre's contact details updated
Glossary	10	Updated
7.3.1, Table 2	27	Error was corrected in the titrating regimen for lamotrigine.
7.3.2, Table 3	27	Minor formatting edits
8.5	33	To appropriately reflect the trial management the following text was removed: ii) "collected by Research Nurses from each hospital's patient administration system (PAS)" and replaced with "accessed as Hospital Episode Statistics (HES) data via the Health and Social Care Information Centre". iii) "PAS" and replaced with "HES".
11.3	49	Text amended to specify the return timeframe for consent
18	63	Table with Summary of changes to protocol with Substantial Amendment 7

18.6 Version 6.0 (19/05/2017)

Summary of changes to protocol with Substantial Amendment No.14:

Section	**Page Number**	**Description of changes**
Protocol Approval	2	Lead Statistician contact details updated
Contact Details	5	Institutions contact details updated

Table of contents	7 - 9	Table of contents updated
1	11	Exclusion criteria clarified and study duration updated
5	22	New section added
6	24-25	For clarity text about eligibility confirmation was amended. Minor corrections to text
7.1	26	Updates to text
8	29-34	Updates to text throughout the section
9.6	37	Minor corrections to text
10	38-47	Definition for SUSAR added. Corrections throughout. Reporting flowchart amended.
13.2 - 13.3	53 - 54	Minor corrections to text
13.8	56	Minor corrections to text

18.7 Version 7.0 (23/08/2017)

Summary of changes to protocol with Substantial Amendment No.16:

Section	Page Number	Description of changes
Table of contents.	7	Updated.
8.1	30	Table 5. Trial assessments updated to allow follow-up questionnaires issue at site during routine clinic visits.
8.4	32	Text updated to allow follow-up questionnaires issue at site during routine clinic visits.
18	64	Summary of changes in protocol with Substantial Amendment 16 added in.

18.8 Version 8.0 (28/11/2018)

Summary of changes to protocol with Substantial Amendment No. 25:

Section	Page Number	Description of changes
signatories	2	Change to UoL sponsor representative signatory due to retirement of Prof Walley and change to Walton Centre Sponsor representative signatory
Contact details	6	Change to UoL sponsor representative due to retirement of Prof Walley and change to Walton Centre sponsor reprsentative
4.2	21	Change to secondary outcomes
8.4	31	Quality of Life and Utility Assessments updated
8.7	34	Text updated
9.6	36 - 37	Updates to text throughout section due to change in secondary outcomes (section 4.2)

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20 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 (Lamotrigine, Zonisamide, Levetiracetam, Valproate)
- Patient Questionnaires (age and time point-specific versions)
- Participating centres list