

**THE  
INTERNATIONAL COLLABORATIVE  
INFANTILE SPASMS STUDY  
(ICISS)**



**PROTOCOL FOR A  
RANDOMISED TRIAL  
IN THE MEDICINAL TREATMENT OF INFANTILE SPASMS**

**Trial Identification Numbers:**

Sponsor's Protocol Code Number:	RD01273	assigned 06/02/2006
ISRCTN:	ISRCTN54363174	assigned 03/04/2006
EUDRACT Number:	2006-000788-27	assigned 08/02/2006
Current Protocol Version Number:	1.3	
Protocol Date:	5 <sup>th</sup> January 2011	
UK MREC Number:	06/MRE06/21	

Protocol Amendment Number	1	2	3		
Protocol Date	05/04/2006	19/12/2006	05/01/11		
New protocol version number	1.1	1.2	1.3		

Signature of the Chief Investigator or Principal Investigator: .....

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## 1. GENERAL INFORMATION

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## 2. GLOSSARY

ACTH	Adrenocorticotrophic Hormone
AED	Anti-Epileptic Drug
ANOVA	Analysis of Variance
CRF	Case Report Form
CTA	Clinical Trial Authorisation
DMEC	Data Monitoring and Ethics Committee
EMA	European Medicines Agency
EU	European Union
EUCTD	European Union Clinical Trials Directive
EUDRACT	European Clinical Trials Database
GCP	Good Clinical Practice
ICISS	International Collaborative Infantile Spasms Study
IMP	Investigational Medicinal Product
MHRA	Medicines and Healthcare products Regulatory Agency
MREC	Multicentre Research Ethics Committee
R&D	Research and Development
SOPs	Standard Operating Procedures
SPC	Summary of Product Characteristics
TMG	Trial Management Group
TSC	Trial Steering Committee
UKISS	United Kingdom Infantile Spasms Study
VABS	Vineland Adaptive Behaviour Scales

### 3. SUMMARY

ICISS is a multicentre randomised parallel group trial investigating the medical treatment of Infantile Spasms (including West syndrome). It will involve centres in Europe, Australia and New Zealand and possibly elsewhere.

ICISS will compare hormonal treatment (either tetracosactide depot or prednisolone) and vigabatrin given together (combined treatment) to hormonal treatment alone.

ICISS builds on the United Kingdom Infantile Spasms Study (UKISS), the infrastructure that supported it and Westdelphi, the international consensus on definitions and outcomes in Infantile Spasms, all research co-ordinated from Bath, UK.

The main early outcome is control of spasms. The main late outcome is developmental progress at 18 months of age. Wherever possible, the infant's epilepsy and developmental outcome will also be assessed at 42 months of age. Permission will be obtained to approach the families to request new ethical consent to reassess the infant's development and epilepsy later in childhood, if worthwhile. Allocation of treatments will be performed over the web. The trial will recruit for approximately 4 years.

### 4. BACKGROUND INFORMATION

#### 4.1 INTRODUCTION

Infantile Spasms are a form of severe epilepsy that affect approximately 1 in 2,250 infants. Infantile Spasms usually present in the first year of life. It can be difficult for both parents and health professionals to realise that something is wrong and to recognise the spasms as an abnormal event. Confirmation of the diagnosis requires an EEG. In Infantile Spasms, the EEG is severely abnormal. It often shows hypsarrhythmia but may show supportive features of the diagnosis of infantile spasms without showing the full features of hypsarrhythmia. Such EEGs are often described as modified or atypical hypsarrhythmia. The term Infantile Spasms includes the more specific subset of infants described as having West syndrome. West syndrome is defined as those infants with Infantile Spasms who are said to have hypsarrhythmia on the EEG.

In Infantile Spasms there is a high risk of underlying neurological disease that independently causes delayed development and other seizure disorders, both of which can be severe. Examples of such disorders include brain damage during pregnancy or childbirth, chromosomal disorders such as Down syndrome and genetic disorders such as tuberous sclerosis. There is a high risk of a poor outcome even when there is apparently no underlying neurological disorder and development is normal before the onset of spasms. In some children, Infantile Spasms may disappear only to be replaced by other seizure types and other severe epilepsy syndromes e.g: Lennox – Gastaut syndrome.

Therapeutic success has traditionally been defined as the elimination of the spasms. Some clinicians also prefer the associated EEG abnormality to disappear. It is still not clear whether, or when, it is necessary to see the EEG improve in order to enhance either developmental or

epilepsy outcome. It is clear that continuing hypsarrhythmia may be due to spasms continuing unrecognised and careful assessment of such infants is required.

Until the mid 1990's, hormonal treatment (either ACTH or prednisolone), was the most frequently used treatment for Infantile Spasms. ACTH has since been replaced by tetracosactide depot – a synthetic alternative. In the 1990s, vigabatrin, a synthetic inhibitor of gaba-amino transferase, was first marketed and was the first anticonvulsant to be effective in controlling Infantile Spasms.

Prior to the United Kingdom Infantile Spasms Study (UKISS), only observational evidence suggested that developmental outcome might be improved by better initial control of spasms. It was widely accepted that infants whose spasms continue despite treatment have a very poor outcome both developmentally and for subsequent epilepsy. This poor outcome may simply reflect a more severe underlying neurological disorder. It may also reflect damage to the developing neurological system being caused by the prolonged uncontrolled epileptic disorder.

## **4.2 UKISS**

UKISS was a study involving 150 hospitals in the UK. The main comparison was between hormonal treatments (either tetracosactide depot or prednisolone) and vigabatrin. Relatively high doses of all treatments were used to minimise the risk of failing to detect a real benefit because of under-dosing. The optimal doses for both prednisolone and tetracosactide depot are not known. Doses of prednisolone at 2 mg/kg (as used in the USA) were known to be less effective than “usual” doses of ACTH. Higher doses of prednisolone were often used in the UK. UKISS gave a high dose short duration of prednisolone or tetracosactide depot, both independent of body weight or surface area. Short duration of hormonal treatment is believed to reduce the risk of adverse reactions.

### **4.2.1 UKISS EARLY OUTCOME**

Between July 1999 and December 2002, 107 infants were allocated a randomised treatment *Lancet* (2004;364:1773-78). The main early outcome measure was control of spasms at Day 14. This was found to be significantly different between the two treatment groups analysed on an intention to treat basis (hormonal treatment, 40 out of 55 [73%] [prednisolone 21 out of 30, tetracosactide depot 19 out of 25] and vigabatrin, 28 out of 52 [54%]; difference 19%: 95% confidence intervals 1% to 36%,  $p=0.043$ ). Following treatment, more infants allocated hormonal treatment lost the features of hypsarrhythmia.

### **4.2.2 META-ANALYSIS OF EARLY OUTCOME**

These results were similar to those from a trial from Italy also comparing ACTH with vigabatrin. If we combine the results from both trials using a fixed effects meta-analysis, the results give improved confidence that hormonal treatments are superior to vigabatrin in stopping spasms (difference 22%: 95% confidence intervals 7% to 38%).

### **4.2.3 UKISS DEVELOPMENTAL OUTCOME AT 14 MONTHS**

The main late outcome measure was development. The infants in UKISS were followed up at 14 months of age to determine development using the Vineland Adaptive Behavioural Scales (VABS) and epilepsy outcome (*Lancet Neurol* 2005; 4: 712-717). They show no difference in the number without spasms at 14 months of age (hormonal 41/55 [75%], vigabatrin 39/51 [76%]) or in development at 14 months (mean VABS composite score: hormonal 78.4, vigabatrin 77.5). However, there was an interaction between treatment and aetiology. The subgroup of infants with no known aetiology shows a difference in development of a size to be clinically important (hormonal 88.2, vigabatrin 78.9,  $p=0.025$ ). These findings lend support to the hypothesis that earlier control of spasms improves developmental outcome.

### **4.2.4 UKISS DEVELOPMENTAL OUTCOME AT A MEDIAN AGE OF 4.2 YEARS**

Due to the significance of these findings, follow up was repeated at a median age of 4.2 years. Most infants have been traced and the parents of 77 infants took part. Nine infants had died. In the subgroup of infants with no identified aetiology, development remains better in those allocated hormonal treatment than vigabatrin [Median VABS (IQR) was 96 (54-102),  $n=21$  and 63 (38-91),  $n=16$ ; Wilcoxon Rank Sum test  $p=0.033$ ]. The size of the difference has increased. Based on the 14 month assessment, more severely affected infants had been lost to follow up in the group allocated vigabatrin.

## **4.3 POTENTIAL SERIOUS ADVERSE REACTIONS: VIGABATRIN**

### **4.3.1 RISK OF VISUAL FIELD DISORDER**

In the 1990's when vigabatrin was first used for the treatment of Infantile Spasms, it was frequently continued for many months or even years after the onset of Infantile Spasms in order to prevent relapse. This was sometimes done even after the addition of hormonal treatment was required because of failure to respond to vigabatrin alone. Then it was discovered that vigabatrin could cause a visual field defect in one third of adults after six months treatment. The risk for infants is not known because a reliable method does not exist of detecting such defects in children under the age of about 11 years. In UKISS, vigabatrin was continued until 14 months of age unless this was not the local clinician's normal practice. In the treatment of Infantile Spasms, many clinicians thus began to use vigabatrin for shorter periods. One observational study suggests that withdrawal after 6 months treatment is not associated with relapse. However, even shorter periods of treatment would appear wise. In UKISS, nearly all first relapses occurred within the first 3 months. With our current knowledge, initial treatment with vigabatrin for at least 3 months but for less than 6 months would seem most appropriate. Continuation subsequently should then depend on the balance of risk, only being justified by a recurrence of spasms.

Therefore, ICISS will begin to withdraw vigabatrin at 3 months completing this by 4 months after trial entry. Subsequent treatment would be at the discretion of the treating clinician and would not be part of the trial protocol.

#### **4.3.2 POTENTIAL EFFECT ON DEVELOPMENT**

In UKISS, infants with no identified aetiology allocated hormonal treatment had better subsequent development. The most likely explanation is that this was due to better initial control of spasms by hormonal treatment. It is possible that the difference in development was due to an adverse effect on development from vigabatrin. Either drowsiness or poor vision would both provide a biologically plausible, if unlikely, mechanism for worse development. In animals, apoptosis is said to occur during development from anti-epileptic medications including vigabatrin. However, in UKISS, normal development (including Vineland composite score of above 100) occurred in some individuals after 9-10 months treatment with vigabatrin, making this explanation unlikely.

### **4.4 POTENTIAL SERIOUS ADVERSE REACTIONS: HORMONAL TREATMENTS**

#### **4.4.1 INFECTION**

Hormonal treatments reduce the infant's ability to fight infection and reduce the response to infection. This makes it more difficult for parents and health professionals to recognise the signs of infection. The diseases with which Infantile Spasms are associated may also increase the risk of infection. Deaths from infection occur in infants without Infantile Spasms but hormonal treatments are thought to increase the risk of death from infection.

#### **4.4.2 POTENTIAL EFFECT ON DEVELOPMENT**

Use of hormonal treatment in the sickest preterm infants, those with severe chronic lung disease, has been associated with a worse developmental outcome. In UKISS no evidence was seen to support such an effect.

### **4.5 RATIONALE FOR ICISS**

Treatments need to be tested against the hypothesis that the new treatment regime will lead to more infants with cessation of spasms and improved development. No treatments other than prednisolone, tetracosactide depot and vigabatrin have been shown to have such good effects on cessation of spasms in more than one study. No other treatments have been systematically examined for developmental outcome. There is potential for benefit in combining both treatments and some infants in UKISS received both treatment at the same time without any identified adverse reaction. No other combination of treatments seems more likely to result in an improved outcome without additional adverse reactions. This approach is also supported by the observation that when an infant fails to respond to the first treatment, there remains a good chance of response to the second treatment. Information from UKISS also suggests that it is not possible to identify, in the first week of treatment, infants who will definitely respond to hormonal treatment. This means it is not possible to identify infants who do not need to be exposed to vigabatrin in combination with hormonal treatment from the outset.



## 5. TRIAL OBJECTIVES, PURPOSE AND DEFINITIONS

### 5.1 OBJECTIVE

To determine whether hormonal treatment combined with vigabatrin is superior to hormonal treatment alone.

### 5.2 PURPOSE (HYPOTHESIS)

The purpose of the trial is to test the following two primary hypotheses:

1. In Infantile Spasms (including West syndrome), combined treatment with both hormonal treatment and vigabatrin is superior to hormonal treatment alone in eliminating spasms.
2. In Infantile Spasms (including West syndrome), combined treatment with both hormonal treatment and vigabatrin results in better development at 18 months of age than hormonal treatment alone. This effect may only be seen in those infants with no identified aetiology for their spasms.

Secondary hypotheses in those infants allocated combined treatment compared to those allocated hormonal treatment alone:

1. Number of infants with elimination of spasms and disappearance of the EEG appearance with which it is associated will be better.
2. Time to elimination of spasms will be shorter (see 9.1.3).
3. Outcomes will be no different if single spasms without clusters are allowed from Day 14 to 42 inclusive in responders.
4. Epilepsy outcomes at 18 and 42 months of age will be better.
5. Developmental outcome at 42 months of age will be better. This effect may only be seen in those infants with no identified aetiology for their spasms.

### 5.3 DEFINITIONS

- **Day 0** – The day of allocation of the randomised treatment. This may not be the same as the day treatment commenced, if randomisation occurred late in the day.
- **Responders** are those with **cessation of spasms** defined as no witnessed spasms (either clusters or single spasms) from Day 14 to Day 42 inclusive.
- **Relapse** only occurs after Day 42 when a cluster of more than one spasm is reported. No EEG is required.
- **Non-responders** are those who have spasms (clusters or single spasms) on any day between Day 14 and Day 42 inclusive.
- **No identified aetiology** – no underlying cause identified after scrutiny of history, examination, and appropriate investigations which must include cranial imaging, preferably MRI (but CT is acceptable) and a metabolic screen. Information obtained

during follow up to age 18 months will be included. Developmental delay without identified cause is not included as an identified cause. Classification will be using the paediatric adaptation of ICD 10. New diagnoses, such as gene mutations, not available until recently, will not be included in the subgroup of infants with identified aetiology to allow comparison with UKISS. An estimate will be made of the significance of new aetiologies identified.

## 6. TRIAL DESIGN

### 6.1 OUTLINE DESIGN

ICISS is a pragmatic parallel group randomised trial comparing hormonal treatment combined with vigabatrin to hormonal treatment alone in the treatment of Infantile Spasms. It will be analysed by intention to treat. The hormonal treatment will be randomly allocated whenever possible.

### 6.2 CONSENT & RECRUITMENT

Infants will be recruited from as many hospitals in the UK as are able and willing to take part. Hospitals in the European Union, Australia and New Zealand and possibly elsewhere will recruit into the trial as soon as their local ethics approvals, data protection approval, responsibility for local sponsorship, indemnity and any other local statutory issues are satisfactorily organised. There is no maximum number of infants to be enrolled per site. Informed signed consent will be obtained for each child.

### 6.3 DURATION OF INVOLVEMENT

Expected duration of trial periods for subject participants are as follows:

- Daily record keeping for the first 42 days.
- Once a month record keeping from Day 42 until 18 completed months of age with three monthly collection of the data.
- Developmental and epilepsy assessment at age 18 and 42 months.
- The minimum duration of treatment with vigabatrin is 14 days – the maximum duration is 4 months.
- The duration of treatment with hormonal treatments is 29 days.
- Follow up at 42 months will be undertaken in the UK and elsewhere this is possible, at least until the results on the early main outcome measure, cessation of spasms, show that this is worth continuing. This will leave over 12 months to raise the necessary finance to follow all infants in the UK and elsewhere this is possible to age 42 months.
- Beyond age 42 months, further assessment of outcomes will only take place if earlier results suggest this is worthwhile, funding is secured and further consents, including ethical consent, are obtained.

## **6.4 OUTCOME MEASURES (Described in detail in Section 9)**

### **6.4.1 PRIMARY OUTCOME MEASURES**

There are two primary outcome measures:

1. The primary **early outcome** will be the cessation of spasms.
2. The primary **late outcome** will be development at 18 months of age.

### **6.4.2 SECONDARY OUTCOME MEASURES:**

1. Absence of spasms on days 13 and 14.
2. Electro-clinical response.
3. Extended electro-clinical response.
4. The time taken to absence of spasms.
5. The number of responders if single spasms are allowed in responders from Day 14 to 42 inclusive.
6. Adverse reactions.
7. Epilepsy outcome at 18 months of age.
8. Development at 42 months of age.
9. Epilepsy outcome at 42 months of age.

## **6.5 PRE-RANDOMISATION STRATIFICATION**

Pre-randomisation stratification will be undertaken in an attempt to balance the treatment groups for factors that may affect development. The factors will be:

1. Risk of developmental delay (yes/no) using the series of questions adapted from UKISS.
  - A proven chromosomal abnormality.
  - A proven dysmorphic syndrome diagnosis.
  - A diagnosis of cerebral palsy made before the onset of spasms.
  - A diagnosis of neonatal encephalopathy with seizures (hypoxic ischemic encephalopathy in a term infant).
  - A diagnosis of delayed development already made before the onset of the spasms. The diagnosis should have been made by either a medical practitioner or a health visitor (specialist children's nurse).
2. Choice of hormonal treatment, if not randomly allocated (prednisolone or tetracosactide depot).

## **6.6 ALLOCATION OF TREATMENTS**

The treatment allocation sequences will be produced by a statistician otherwise independent of the trial and held on a secure database. Those involved with the treatment allocation will **not** have access to the randomisation sequences.

The hormonal treatment will be allocated randomly in the UK and elsewhere this is possible, depending on the availability of both hormonal treatments, parental choice and, rarely and specified below, clinical preference. In order to protect recruitment into the trial for the main comparison of combined treatment against hormonal treatment alone, centres and clinicians only willing to take part in the trial if they can choose the hormonal treatment (clinical preference) will only be allowed to do so if the members of the Trial Steering Committee (TSC) cannot persuade them to randomly allocate the hormonal treatment. They will not be allowed to take part in the trial if they wish to make this choice for individual patients – only if they wish all patients at their centre to have one of the two hormonal treatments. Parents will always be allowed to choose the hormonal treatment if they do not wish it to be randomly allocated.

In centres where the clinician will only take part in the trial if they can choose the hormonal treatment, parents may wish to exercise their right to choose the other hormonal treatment (if available). Clinicians in these centres will have to accept this as a result of informed choice.

Allocation of treatments will take place via the trial website.

## **6.7 BLINDING**

- Blinding of the clinical outcomes will not be possible.
- Blinding of vigabatrin will not be undertaken because of the cost involved.
- Blind reporting of the EEGs will be undertaken.

## **6.8 TRIAL STOPPING RULES**

An interim analysis will not be undertaken. The differences required to consider stopping are so extreme that it is not considered appropriate to lose power by doing so.

## **6.9 ARRANGEMENTS FOR ADHERENCE TO GOOD CLINICAL PRACTICE**

This trial will adhere to the principles of good clinical practice as stated in European Commission Directive 2005/28/EC.

## **6.10 ARRANGMENTS FOR TRIAL SUPPLIES**

No specific arrangements have been made for the supply of the treatments, as these are all licensed medicinal products. All three treatments are in regular use for the treatment of Infantile Spasms.

## 6.11 DEFINITION OF END OF TRIAL

The definition for the ends of the trial will be:

- Drug regulatory approval will continue until all participants have finished mandatory treatment with any of the Investigational Medicinal Products.
- Ethics approval will continue until developmental and epilepsy follow up has been completed in the last child at 42 months of age.
- R&D approval will continue until analysis, publication and archiving are complete.

## 6.12 PROTOCOL AMENDMENTS

In the UK, substantial protocol amendments will be notified, by the CI, to the MREC, MHRA and the Sponsor's R&D Department. They will be itemised in a protocol appendix (no 1) and detailed on the front page of the protocol. Principal investigators, their ethics committees and R&D departments (or equivalent) will be notified as required.

In sovereign states outside the UK, the equivalent authorities will be notified as required.

# 7. SELECTION AND WITHDRAWAL OF SUBJECTS

## 7.1 INCLUSION CRITERIA (ALL CRITERIA MUST BE MET)

- The clinical features of Infantile Spasms confirmed by the consultant in charge or his/her nominated deputy.  
*This implies that the ictal manifestations are compatible with the diagnosis of infantile spasms.*
- An EEG that is hypsarrhythmic or similar, compatible with the diagnosis of Infantile Spasms.  
*If a standard awake EEG is not compatible with the diagnosis of infantile spasms, a sleep EEG is required to do so. Video EEG is preferred but is not required.*
- Signed informed consent has been given.

## 7.2 EXCLUSION CRITERIA

- More than 7 days has elapsed since the diagnosis was made through the combination of the EEG result and confirmation of the clinical features by the consultant in charge or his/her nominated deputy.
- Age less than two months or greater than one year and two months.
- A diagnosis or high risk of tuberous sclerosis  
*(known affected parent, previously diagnosed cardiac rhabdomyoma, hypomelanotic macules, forehead fibrous plaque, shagreen patch, retinal phakoma or known polycystic kidneys).*
- Previous treatment for Infantile Spasms other than a therapeutic trial of pyridoxine to exclude pyridoxine dependent seizures (see Section 8.2).  
*Note - previous treatment for other seizure types is **not** a reason for exclusion.*

- Previous treatment (within the last 28 days) with vigabatrin or hormonal treatments.
- A contraindication to vigabatrin or hormonal treatments.  
*A risk of a visual field defect is not considered a contraindication.*
- A lethal or potentially lethal condition, other than Infantile Spasms, with a risk of death before 18 months of age.
- Doubt about the ability of the parents or guardians to know when the spasms stop.  
*This is likely to include parents known to be intravenous drug abusers.*
- Unavailable for follow up to 18 months of age.
- Those enrolled in a concurrent trial that is still in the active phase.
- The language ability of the parents or guardians is such that they may not understand what is being requested of them.
- The language ability of the parents or guardians is such that it will not be possible to undertake the Vineland assessment.

### 7.3 WITHDRAWAL OF SUBJECTS

**No patient may be withdrawn by the principal investigator or local clinician once entered into the trial unless it is in the infant's or parent's best interest to do so.**

The treatment may be changed at any time if it is in the infant's best interest to do so. The decision must be justified for reasons other than spasms continuing or getting worse within the first 14 days as response can occur in the final days of treatment and can be abrupt.

**Parents or guardians may withdraw their child from the trial at any time without giving a reason and without affecting the care they receive.**

Good clinical practice requires us to ask if we can be told why the child is being withdrawn.

Those wishing to withdraw from the study will be asked if they are willing to clarify the following:

- Do they wish to withdraw from the trial completely or just from a part of the trial, such as the treatment allocated?  
*Withdrawal of the allocated treatment at the request of the parent or guardian is not withdrawal from the trial but a protocol violation. The infant may continue in the study if the parents are happy to do so.*
- Can we approach them in clinic or by telephone for either the developmental or epilepsy assessments when their child is 18 months of age, without asking them for information at any time in between?
- Do they wish to continue to receive the parent newsletters from the trial centre?
- Do they wish to inform us of the reason for withdrawing from the trial as it is good practice for us to report the reason?

## 8. TREATMENT OF SUBJECTS

Dosages are those that were used in UKISS and are proposed to maximise both the speed of response and the number of responders.

### 8.1 TIME BETWEEN DIAGNOSIS AND TREATMENT ALLOCATION

Infants should be enrolled into the trial as soon as possible but sufficient time must be given to the parents/guardians to allow them to read the information about Infantile Spasms and the trial before consent is obtained. See also exclusions, Section 7.2.

### 8.2 TREATMENT WITH PYRIDOXINE BEFORE ALLOCATION OF A RANDOMISED TREATMENT

The possibility of pyridoxine dependent seizures may be considered before offering a trial treatment. **We suggest** that a therapeutic trial for pyridoxine dependent seizures is only necessary in those infants:

- with additional seizure types, *and*
- where no other cause for their spasms is known.

Please note the child is excluded from entry to the trial if pyridoxine is given as a treatment for infantile spasms when you are **not** considering the diagnosis of pyridoxine dependent seizures (Section 7.2).

### 8.3 MANUFACTURERS INFORMATION (UK)

**Vigabatrin** is marketed in the UK by Sanofi-Aventis, Guildford, UK and is supplied in sachets of 500 mg. Sachet contents may be placed in a beverage (e.g. water, fruit juice or milk) immediately before oral administration.

**Prednisolone** is marketed in the UK by Sovereign Medical, Basildon, UK as soluble prednisolone tablets each containing 5mg.

**Tetracosactide depot** is marketed in the UK by Alliance Pharmaceuticals, Chippenham, UK as Synacthen Depot for intramuscular injection. 0.5 mg of tetracosactide acetate is approximately equivalent to 40 international units. In the UK, 1 ml contains 1 mg.

## 8.4 TREATMENT FROM DAY 0 TO DAY 14

**ALL infants will receive a hormonal treatment.**

**Those allocated vigabatrin will receive combined treatment with both vigabatrin AND hormonal treatment given at the same time.**

### 8.4.1 VIGABATRIN TREATMENT ROUTE AND DOSE

Vigabatrin is given orally, **twice a day**. We recommend that each sachet of 500 mg of vigabatrin is made up in 10 ml of water making a mixture containing 50 mg per ml water. Use the infant's weight on Day 0 (the day of allocation of randomised treatment) to calculate the dosages for the first 14 days. The dosage will be given to the nearest 25 mg dose (0.5 ml), i.e. round up or down to the nearest 0.5 ml.

The dose escalation is as follows:

1. The initial two doses to be 25 mg/kg per dose.
2. All infants will increase to 50 mg/kg per dose given twice a day for a further 72 hours (a further 6 doses).

At 96 hours after the start of treatment (ie after the first 8 doses of vigabatrin), if any spasms have occurred in the previous 24 hours, **or** if spasms reappear after this but before Day 14, increase the dose to 75 mg/kg per dose given twice a day (150 mg/kg per day).

### 8.4.2 HORMONAL TREATMENT (PREDNISOLONE OR TETRACOSACTIDE DEPOT) ROUTE AND DOSE

#### 8.4.2.1 Prednisolone

Prednisolone is given orally, 10 mg **four times a day** for 14 days unless:

If spasms continue on Day 7 **or** reappear between Day 8 and Day 14 inclusive, increase the dose to 20 mg **three times a day** for the remaining doses.

#### 8.4.2.2 Tetracosactide Depot

**Tetracosactide depot must only be given by a doctor or nurse aware of the potential for allergic reactions and with the necessary equipment, backup and skills to manage this – although at the age of the trial participants, severe allergic reactions are very uncommon. It is expected that it will be given in healthcare premises and not at home. If any local or systemic reaction occurs during or after an injection (for example, marked redness and pain at the injection site, urticaria, pruritus, flushing, faintness or dyspnoea) do not give a further dose.**

Tetracosactide depot is given by intramuscular injection, 0.5 mg **on alternate days** (Days 0, 2, 4, 6, 8, 10, 12, 14) unless:

If spasms continue on Day 7 **or** reappear between Day 8 and Day 14 inclusive, increase the dose to 0.75 mg **on alternate days** for the remaining doses.



## **8.5 TREATMENT AFTER DAY 14 IN THOSE WITH NO SPASMS ON AND BETWEEN DAYS 14 AND 42 INCLUSIVE.**

### **8.5.1 HORMONAL TREATMENT**

Hormonal treatment should reduce as follows:

If receiving either prednisolone at 10 mg four times a day or tetracosactide depot 0.5 mg alternate days on Day 14, then the prednisolone dose will be:

- 30 mg daily for five days, then
- 20 mg daily for 5 days and finally
- 10 mg daily for 5 days.
- Prednisolone will then stop.

If receiving prednisolone at 20 mg three times a day or tetracosactide depot 0.75 mg alternate days on Day 14, then the prednisolone dose will be:

- 40 mg for 5 days, then
- 20 mg daily for 5 days and finally
- 10 mg daily for 5 days.
- Prednisolone will then stop.

### **8.5.2 VIGABATRIN TREATMENT IN THOSE ALLOCATED COMBINED TREATMENT (BOTH VIGABATRIN AND HORMONAL)**

Those potential responders allocated combined treatment with hormonal treatment and vigabatrin are required by the protocol to receive vigabatrin after Day 14 as follows (in addition to their tailing dose of prednisolone):

Vigabatrin treatment will continue at the same dose on a body weight basis, increasing as the body weight increases, in increments of 25 mg per dose (50 mg per day) as required until 3 calendar months from Day 0. The vigabatrin will then be withdrawn over the next four weeks. At the start of each week it is being withdrawn, the dose will be reduced by as close as possible (to the nearest 25 mg or 0.5 ml) to one fifth of the maximum total daily dose being given prior to the commencement of the reduction.

## **8.6 TREATMENT AFTER DAY 14 IN THOSE WITH SPASMS ON OR AFTER DAY 14.**

### **8.6.1 NON RESPONDERS:**

Treatment after Day 14 in non responders is **not** mandated by the protocol. Clinicians wanting advice on further treatment should contact their specialist colleagues.

## **8.6.2 RELAPSE IN RESPONDERS**

Treatment after Day 42 in responders who then relapse is **not** mandated by the protocol. Clinicians wanting advice on further treatment should contact their specialist colleagues.

## **8.7 MEDICATIONS PERMITTED AND NOT PERMITTED, INCLUDING RESCUE MEDICATION, BEFORE AND/OR DURING THE TRIAL**

Rescue medication can be given for the management of other epileptic seizures. Preventative anti-epileptic treatment for other seizure types should be continued wherever possible at the same dose for the first 14 days. No other treatment for Infantile Spasms is allowed in the first 14 days. All other medications are permitted.

## **8.8 TREATMENT IN AN INFANT WITH NO CLINICAL EVIDENCE OF CONTINUING SPASMS BUT WITH HYPARRHYTHMIA OR SIMILAR ON THE FOLLOW UP EEG.**

Management in this trial is **only** on the basis of clinical evidence of Infantile Spasms. We do not recommend treating EEG findings. The reasons are as follows:

Resolution of hypsarrhythmia (or features compatible with the diagnosis of Infantile Spasms) does not always occur on the same day as clinical spasms disappear. Finding hypsarrhythmia may be related to the day on which the EEG is performed. In addition, there is no evidence as yet that the infant's prognosis is improved if treatment is given when the EEG is hypsarrhythmic but the infant is thought to have stopped having spasms. Hypsarrhythmia is thought to disappear more quickly in those treated with hormonal treatment rather than vigabatrin but the significance of this is not known.

If the Day 14 EEG suggests that hypsarrhythmia continues, we suggest that clinicians confirm that there really is no evidence of continuing spasms. How this is done is at the discretion of the principal investigator. Procedures to consider include:

- Repeating the EEG after an interval if it seems likely the spasms have disappeared on clinical grounds.
- Performing a video EEG to look for evidence of subtle spasms.
- Admission to hospital for closer observation.

## **8.9 DRUG ACCOUNTABILITY**

We are monitoring drug accountability by direct questioning only. As this is a pragmatic trial, some dosage errors are expected which are not believed to have a measurable effect on our outcome measures. Investigators will report, at the Day 15 and Day 43 assessments, the answer to the question "Was the allocated treatment given accurately according to the protocol?". The response to this question will be based on direct communication between the investigator and the parent/carer.

## **8.10 MONITORING EXPOSURE TO TRIAL TREATMENTS AFTER DAY 42**

### **8.10.1 EXPOSURE TO HORMONAL TREATMENT**

Each course of hormonal treatment will be reported to the trial centre indicating whether hormonal treatment has been given (yes/no) in any calendar month from Day 42 to age 18 months. This may be helpful in interpreting the risk of serious adverse events from repeated hormonal treatment, if any, during the follow up period.

### **8.10.2 EXPOSURE TO VIGABATRIN**

Prescription of vigabatrin will be recorded (yes/no) for each calendar month from Day 42 to age 18 months. This may be helpful in case of later analysis of vision.

## **8.11 FREQUENCY OF ASSESSMENTS BY PRINCIPAL INVESTIGATOR**

Assessments for the purpose of completing CRFs should be made by the principal investigator as a minimum on Days 0, 15, 43 and thereafter at 3 monthly intervals to age 18 months. The 3 monthly assessments can be undertaken by telephone if this is considered appropriate because the infant is doing well.

Other contacts will be needed during the first 14 days both for good clinical management and in order to comply with the protocol e.g. any day when the dose may need to be increased if spasms are continuing or have re-appeared.

# **9. ASSESSMENT OF EFFICACY**

## **9.1 EARLY OUTCOME**

### **9.1.1 PRIMARY EARLY OUTCOME**

Responders are those with *cessation of spasms*, defined as no witnessed spasms (clusters or single spasms) from Day 14 to Day 42 inclusive.

Assessment of response will be by daily report from the primary carer (parent, guardian or health professionals) of the presence or absence of any witnessed spasms. The daily report will be assessed by the principal investigator or his appointed deputy at regular follow up appointments which should include appointments as soon after Day 14 and Day 42 as possible. The daily report should be supported by a diary wherever possible, but it is the principal investigator's interpretation of the events recorded in the diary and reported that is to be used in the assessment of primary clinical outcome.

### 9.1.2 ELECTRO-CLINICAL OUTCOME & BLIND ASSESSMENT OF EEGS

- *Electro-clinical response* is defined as *cessation of spasms* with the addition of:  
Absence of hypsarrhythmia **and** absence of the EEG features which confirm the diagnosis of Infantile Spasms on the Day 14 EEG. Valid Day 14 EEGs will be those undertaken between Day 14 and Day 21 inclusive.
- *Extended electro-clinical response* is defined as *electroclinical response* with the addition of:  
Absence of hypsarrhythmia **and** absence of the EEG features which confirm the diagnosis of Infantile Spasms on the Day 42 EEG. Valid Day 42 EEGs will be those undertaken between Day 42 and Day 49 inclusive. The Day 42 EEG is only required in those with cessation of spasms and is preferred but not required by the protocol.

The Day 14 and Day 42 EEGs should include a period of sleep wherever possible. A video EEG is preferred, but not required by protocol. We will report the number of electro-clinical responders and number of extended electro-clinical responders with an EEG including a period of sleep.

The EEG results will be available to the local clinicians through their normal practice. The Day 0, 14 and 42 EEGs will subsequently be evaluated blind to the identity of the infant, the recruiting centre, the trial treatment and the clinical outcome. This will be done by an evaluation group of 3 individuals. A majority view will be accepted if a unanimous view is not possible. The whole EEG recording will be assessed wherever possible. If this is not possible, a 30-60 second printed sample will be assessed. This sample will be chosen by the principal investigator or neurophysiologist as supporting the report of hypsarrhythmia or similar appearance supporting the diagnosis of Infantile Spasms. The assessors will be asked to classify the EEG into four groups:

- Hypsarrhythmia.
- Compatible with Infantile Spasms but not hypsarrhythmia.
- Abnormal but not compatible with Infantile Spasms and not hypsarrhythmia.
- Normal.

Where no blind report is available, the local clinician's report will be used. The number of infants in each group where no blind report is available will be reported.

### 9.1.3 TIME TO NO WITNESSED SPASMS

- Time taken to the first day of no witnessed spasms that continues without subsequent spasms to Day 14 inclusive.
- Time taken to the first day of no witnessed spasms that continues without subsequent spasms to include Day 13 and 14 in all infants. This will allow direct comparison with UKISS.

Both these outcomes will be analysed by examining the number of consecutive days free of spasms preceding and including Day 14.

## **9.2 LATE OUTCOME**

### **9.2.1 PRIMARY LATE OUTCOME: DEVELOPMENT AT 18 MONTHS**

Development will be assessed at 18 months of age using the Vineland Adaptive Behaviour Scales (VABS). We aim to complete 90% of assessments within one calendar month of the planned age and all assessments within 2 calendar months. The VABS will be performed over the telephone or in person using the VABS in the most appropriate language.

The Vineland has four domains (communication, daily living skills, socialization and motor skills) and these can be combined to give an Adaptive Behaviour Composite (ABC) score. The ABC score has a standard score of 100 and a standard deviation of 15. The group means (or medians if not normally distributed) for the ABC score and domain scores will be compared for each treatment group for all infants by intention to treat. We will also investigate to see if there is an interaction between treatment and aetiology (see Section 5.3 for the definition of no identified aetiology).

### **9.2.2 EPILEPSY STATUS BETWEEN DAY 42 AND AGE 18 MONTHS**

Epilepsy status and AED medication will be recorded for each calendar month from Day 42 to age 18 months using the following categories:

- Infantile spasms (clusters of spasms) .
- Any other epileptic seizure including febrile seizures.
- Names of any preventive AEDs prescribed

This information will be used in order to investigate the possibility that any association between initial randomised treatment and developmental outcome is confounded by subsequent seizure status or AED use.

### **9.2.3 EPILEPSY HISTORY.**

A structured paediatric epilepsy history will be taken at 18 months of age and where possible at 42 months of age at the same time as the VABS assessment.

This will record the presence or absence of any epileptic seizure over the previous 28 days, classified into 8 groups:

- Infantile Spasms
- Blank spells
- Drop attacks
- Tonic-clonic (primary or secondarily generalised)
- Focal – without secondary generalisation
- Myoclonic
- Unclassifiable
- Febrile

Seizures will be classified as continuing if present at any time in this period. The frequency of seizures will not be assessed. Prophylactic (preventative) anti-epileptic drug medication (AED)

usage will be documented, recording the name but not dosage. Rescue treatment will not be recorded. Only those AEDs in use during the previous 28 days will be recorded.

The number of infants in each treatment group will be compared by:

- Those with Infantile Spasms.
- Those with febrile seizures.
- Those with one or more seizure type (including Infantile Spasms, excluding febrile seizures).
- Those with two or more seizure types (including Infantile Spasms, excluding febrile seizures).
- Those with three or more seizure types (including Infantile Spasms, excluding febrile seizures).
- Those with one or more antiepileptic medications.
- Those with two or more antiepileptic medications.
- Those on the ketogenic diet at any time during the previous 28 days.
- Those who have had epilepsy surgery (including Vagal nerve stimulation).

There may be an interaction between the number of antiepileptic medications and the number of seizure types and this will be explored.

#### **9.2.4 DEVELOPMENT AT 42 MONTHS**

The assessment of development at 42 months will also use the VABS as stated in 9.2.1.

### **9.3 TIME FROM ONSET OF SPASMS**

There may be an effect on development from the duration of spasms prior to treatment. The exact time of onset may not be certain. The time from onset of spasms, where this is known, to the start of treatment will be recorded in the following categories:

- Less than or equal to one week (7 days)
- More than one week but less than or equal to two weeks (14 days)
- More than two weeks but less than or equal to one calendar month
- More than one calendar month but less than or equal to two calendar months
- More than two calendar months
- Not known or unclear

Where the exact duration is not known and may lie in one of two categories, the greater duration category will be entered.

### **9.4 ADVERSE REACTIONS**

Adverse reactions will be tabulated by treatment allocated and duration in trial (up to Day 14, from Day 15 to Day 42 and from Day 43 to 4 months into the trial), indicating which treatment was believed responsible and whether the local clinician, trial management group, or both thought that the reaction was causally related to the treatment.

## **9.5 SENSITIVITY ANALYSES**

The following sensitivity analyses will be undertaken at the end of the trial:

- An adjustment for the inclusion of any infant where the blind reporting of the pre-treatment EEG by the evaluation panel suggests that the EEG was not supportive of the diagnosis of Infantile Spasms.
- An adjustment for any infant who did not have cranial imaging and where no underlying aetiology has been detected.
- An adjustment will be made for any infant in whom it proved impossible to obtain a Vineland Adaptive Behaviour composite score where a suitable formal developmental assessment undertaken as part of routine care is available.
- An adjustment will be made for infants lost to developmental follow up.

## **9.6 COMPARISON OF PREDNISOLONE AND TETRACOSACTIDE DEPOT**

For those infants where hormonal treatment was allocated randomly, identical outcomes to those of the main comparison will be assessed between prednisolone and tetracosactide depot. A meta-analysis will then be undertaken combining the comparable results from UKISS.

## **9.7 STUDY OF EEG FEATURES OF INFANTILE SPASMS**

These EEG assessments will not form part of the reporting for the clinical trial. They will be reported as a separate study within ICISS. The results may inform study design for future trials of medicinal treatment of Infantile Spasms.

Where a cluster of spasms has been recorded, this will be assessed blind for the presence or absence of hypsarrhythmia between spasms within a cluster. This will be used to test the hypothesis that the presence of hypsarrhythmia between spasms within a cluster is a good prognostic sign. Blind evaluation of the inter-rater and intra-rater variability of specific EEG features associated with Infantile Spasms will be undertaken. An evaluation of the relationship between these features and the clinical features of Infantile Spasms will be undertaken.

## **9.8 ASSESSMENT OF UNDERLYING AETIOLOGY**

Underlying aetiology will be classified using the Paediatric adaptation of ICD 10 and grouped as prenatal, perinatal, postnatal, other and not known. Information from the CRFs will be supplemented by direct questions to the study doctor (local treating clinician) as required. Copies of the brain scans will be obtained wherever possible and will be reported by an expert group to maintain consistency in assessment (see also Section 5.3, Definitions).

## 10. ASSESSMENT OF SAFETY

### 10.1 OVERVIEW OF CLINICAL TRIAL RISK ASSESSMENT AND PHARMACOVIGILANCE

A clinical trial risk assessment will be undertaken by the sponsor prior to commencement of recruitment. A Data Monitoring and Ethics Committee (DMEC) will be appointed by the sponsor. The Trial Steering Committee (TSC) will meet approximately every 3 months and will act as an extended Trial Management Group (TMG).

The trial is being undertaken by a team who have successfully completed a similar trial within the UK. Data collection has been simplified. Translations will be made of all relevant material. Appropriate approvals in each country outside the UK will be made through the appointment of a National Co-Collaborator (the Senior Principal Investigator) in each sovereign state.

### 10.2 PHARMACOVIGILANCE

#### 10.2.1 DEFINITIONS USED FOR REPORTING:

ADVERSE EVENTS	Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does NOT necessarily have a causal relationship with this treatment.
ADVERSE REACTION	All untoward and unintended responses to an investigational medicinal product thought to be related to any dose administered. An assessment of causality by either the treating clinician OR by the TMG will lead to the report of an adverse reaction.
UNEXPECTED ADVERSE REACTION	An adverse reaction the nature of which is not consistent with the applicable product information as defined in the protocol.
SERIOUS ADVERSE REACTION (SAR)	Any untoward medical occurrence or effect that at any dose: <ol style="list-style-type: none"> <li>1. Results in death.</li> <li>2. Is life threatening (at risk of death at the time of the event: not an event which hypothetically might have caused death if it were more severe).</li> <li>3. Requires hospitalisation or prolongation of an existing inpatients hospitalisation.</li> <li>4. Results in persistent or significant disability or incapacity.</li> </ol>
A SEVERE adverse reaction describes the intensity of the event and is not the same as serious.	
SUSPECTED UNEXPECTED SERIOUS ADVERSE REACTION, (SUSAR)	A serious adverse reaction which is not listed in the protocol as expected. It is suspected at the time of reporting – when it is not yet confirmed as an adverse reaction.



## 10.2.2 EVALUATION OF ADVERSE EVENTS AND REACTIONS

Each adverse event will be evaluated by the principal investigator to determine whether in their view it is an adverse reaction. If considered an adverse reaction, it will be reported to the trial centre using the classification stated in the protocol.

The evaluation must immediately include an assessment of whether the reaction is **SERIOUS**.

**Serious adverse reactions must be reported to the trial centre immediately (see 10.4 below).**

If serious, the event must be evaluated for its **expectedness** (is the event listed in Section 10.5).

**If UNEXPECTED (see 10.4.2 below), this becomes a SUSAR and must be reported immediately by the local clinician or principal investigator to the trial centre in Bath, UK. The trial centre will be responsible for notifying the regulatory authorities.**

## 10.3 DURATION OF ADVERSE REACTION REPORTING

Adverse reactions will be recorded and reported from Day 0 until mandatory treatment, according to the protocol, has finished. This will be a minimum of 29 days and a maximum of 4 calendar months after Day 0. Adverse reactions occurring after this time will be recorded but will not be reported to the regulatory authorities because this is the period of follow up and not of mandatory treatment.

## 10.4 SAFETY REPORTING

Adverse reactions should be reported to the trial centre with outcome information unless they are serious when they should be reported as below.

### 10.4.1 SAR REPORTING

All serious adverse reactions must be reported to the trial centre immediately. The trial centre will make its own assessment of causality and expectedness. Serious Adverse Reactions will be reported to the TSC, the sponsor and the DMEC chair. The Chief Investigator, the DMEC Chair and the sponsor can all request a meeting of the DMEC to discuss serious adverse reactions.

### 10.4.2 SUSAR REPORTING BY THE TRIAL CENTRE

Fatal or life threatening SUSARS will be reported not later than **7 days** after the trial centre had information that the case fulfilled the criteria for a fatal or life threatening SUSAR. Follow up information will be reported within a further 8 days.

All other SUSARs will be reported not later than **15 days** after the trial centre had information that the case fulfilled the criteria for a SUSAR.

### 10.4.3 ANNUAL REPORTING

The annual safety report will have an annual data lock point on the anniversary of the first CTA authorisation of the trial by the MHRA.

Annual reports will be submitted within 60 days of this date to:

- The sponsor.
- The relevant ethics committee.
- The MHRA or EMEA.

For all trial participants including those outside the EU, the report will contain,:

- A report on subject safety – to include **new** information not in the protocol on IMPs.
- A line listing of all suspected SARs – including SUSARs.
- An aggregate summary tabulation of suspected SARs.

## 10.5 ADVERSE REACTIONS SPECIFIC TO THE MEDICINES USED IN THIS TRIAL

Adverse reactions are known to be associated with the trial treatments. The reactions listed below, and any others documented in the IMP dossier, will be the expected adverse reactions and will not be reported as SUSARs. Any category of SAR may result from these adverse reactions.

### 10.5.1 HORMONAL TREATMENTS - PREDNISOLONE AND TETRACOSACTIDE DEPOT

**No marketing authorisation exists in the UK for the use of these treatments for Infantile Spasms. This list is derived from that used in our previous trial which was itself derived from adverse reactions mentioned in Medicines for Children:**

- Irritability.
- Hypotonia.
- Hypertonia.
- Increased appetite.
- Weight gain (to include Cushingoid appearance).
- Gastro- intestinal upset.
- Fluid and electrolyte disturbance, including systemic hypertension and its consequences.
- Endocrine and metabolic disturbance, including hyperglycaemia, hypernatraemia and hypokalaemia.
- Neuropsychiatric disturbance including sleep disturbance.
- Infection proven microbiologically, or resulting in a recorded fever above 38 degrees C for more than half an hour or above 38.5 degrees C at any time, or in treatment with antibiotics or *Varicella zoster* infection ( chicken pox) diagnosed clinically.
- Treatment for *Varicella zoster* (chicken pox) exposure.
- Immunosuppression and its consequences.
- Allergic rash (tetracosactide depot only) or anaphylaxis.

## 10.5.2 VIGABATRIN

**A marketing authorisation exists in the UK for this IMP to be used for treatment of Infantile Spasms. The adverse reactions listed in the SPC include those found in adults treated for other conditions. The list below is derived from that used in our previous trial which was itself derived from adverse reactions mentioned in Medicines for Children and the SPC:**

- Drowsiness.
- Hypotonia.
- Increased appetite.
- Weight gain.
- Visual field constriction.
- Infection proven microbiologically, or resulting in a recorded fever above 38 degrees C for more than half an hour or above 38.5 degrees C at any time, or in treatment with antibiotics or *Varicella zoster* infection (chicken pox) diagnosed clinically.
- Gastro-intestinal upset.
- Neuropsychiatric disturbance including sleep disorder.

## 10.5.3 COMMENTS ON SERIOUS ADVERSE REACTIONS SPECIFIC TO THE TRIAL

- 1) Hospitalisation (or prolongation of hospital stay) is sometimes required in infants to determine whether or not an adverse reaction has occurred. This is not the same as a reaction requiring admission to hospital. A good example of this is admitting an infant to allow them to fall asleep so that a blood pressure measurement can be taken that is not raised artificially by crying. Such admissions or prolongations of hospital stay will not be considered as serious adverse reactions even if an adverse reaction is detected as long as the infant is able to be discharged at the level of reaction detected – even if the infant is kept in longer for social reasons e.g. because it is now too late to send such a young infant home.
- 2) Visual field constriction may result in significant disability. It will not be assessed in this trial as no validated method exists to do so until the infants have reached a developmental age of around 9-11 years. Many of the infants will never reach this stage of development because of the high risk of neurodevelopmental problems associated with the problem. A parallel study of new methods of assessment of visual fields may be undertaken in some infants - this will be subject to separate ethical approval and a separate protocol.
- 3) Poor development will not be considered a serious adverse reaction in any individual infant because all the infants are at high risk of poor development without exposure to treatment, it would be difficult to relate this to the trial treatment in any individual infant and development is a main outcome measure.

## 10.6 MANAGEMENT OF SPECIFIC ADVERSE REACTIONS

**Standard management of the following adverse reactions or potential reactions is suggested, but is not required by the protocol. All such management remains the responsibility of the treating clinician.**

- **Systemic hypertension** due to hormonal treatments should be assessed when necessary with the child asleep to obtain a resting measure. Only if the systemic blood pressure is reliably measured and both consistently and significantly above 120 over 90 would we suggest treatment. Young infants seem to tolerate raised blood pressure for the relatively short periods of time they are on hormonal treatment. We do not suggest that you stop the hormonal treatment unless this is considered essential since this may jeopardise the infant's chance of responding to treatment. If treatment for systemic hypertension is required, the addition of a diuretic such as bendrofluazide is usually all that is required. You may need to check the potassium level and consider oral replacement therapy. We suggest checking the infants blood pressure after approximately 48 hours and again 7 days after treatment commences.
- **Infection** must be taken seriously in infants on hormonal treatments since they can suppress the infant's ability to respond to infection and reduce the signs of infection. Infants should be treated using the local unit's protocol for children with neutropaenic fever. Antibiotics should be given promptly for those with a single fever greater than 38.5 degrees C or two measurements of fever greater than 38 degrees C taken more than one hour apart. Appropriate cultures should be taken. Antibiotic cover must include anti-staphylococcal treatment since that is frequently a serious risk in infants on hormonal treatment.
- **Varicella Zoster** infection can be fatal to those on hormonal treatments. If contact with this infection occurs while an infant is on hormonal treatment, you should consider the need for zoster immune globulin. If vesicles appear, the infant should be treated as soon as possible with aciclovir intravenously if still on hormonal treatments.
- **Immunisations.** Live vaccines must not be given to the infants once hormonal treatments have commenced and not until after hormonal treatment has been stopped for at least one month. Consider giving other vaccines as usual but then consider the need for additional doses once the infant has been off hormonal treatment for at least one month because the infant's response may have been sub-optimal while on hormonal treatment.

## 11. STATISTICS

### 11.1 STATISTICAL METHODS

- Primary analysis of data will be by **intention to treat** of all randomised subjects.
- Significance levels will be 5%.
- For binary outcomes, proportions in each treatment arm will be compared by chi square tests.
- For analysis of time to cessation of spasms, actuarial analyses will be undertaken.
- For comparison of continuous outcomes, group means will be compared using t tests unless non-parametric tests are required.
- ANOVA, or similar multivariate analyses, will be undertaken to explore for interactions.
- All deaths and all infants lost to follow up will be reported.

Specifically, we intend to examine for any interaction between treatment and aetiology. Post-stratification analyses will be undertaken to see what effect, if any, the following may have had on the main outcomes:

1. Use of pyridoxine
2. English as the language used for the Vineland assessments.

### 11.2 SAMPLE SIZE AND POWER CALCULATIONS

Power calculations have been undertaken on the primary clinical response and on development, using information from UKISS.

#### 11.2.1 MAIN EARLY OUTCOME: CESSATION OF SPASMS

Within UKISS, the proportions with primary clinical outcome according to the definitions of cessation of spasms to be used in this trial are estimated as 33 of 55 on hormonal treatments (60%) and 22 of 52 on vigabatrin (42%). An improvement to 75% is possible if combined treatment improves both initial control by Day 14 and reduces relapse before Day 42. Drop-outs in this early outcome will be rare.

**The numbers required to see an improvement from 60% to 75% would be 205 in each group assuming 90% power in a two sided test at  $p=0.05$ . (150 would give 80% power)**

#### 11.2.2 MAIN LATE OUTCOME: DEVELOPMENT

In UKISS, VABS score was assessed at 14 months of age and most infants were reassessed at a median age of 4.2 years when the difference in VABS score was even greater. ICISS will assess development at 18 months of age initially and is therefore likely to detect a larger difference in VABS score than UKISS did at 14 months of age. Drop outs are likely to be 5% by age 18

months. No adjustment is made for this as the increased power of assessing development at this age is likely to be significantly greater than 5%.

The difference in development in UKISS was found only in the subgroup with no identified aetiology. In this group, the VABS score was 88 for those on hormonal treatment alone and will need to improve to 95 on both treatments to be of clinical importance. The power to detect this difference is 90% with 85 infants with no cause found in each group, using two sided tests. 85 infants with no cause found will be found within 205 infants in each treatment group. We are likely to see a bigger difference in development between the two groups at 18 months than UKISS found at 14 months. 205 infants in each group will give us 99.75% power to detect a difference of half a standard deviation in the main late outcome comparing the two treatment groups (VABS score increasing from 78.6 (SD 16.8) to 86.1 (SD 15)).

**We will aim for a sample size of 205 in each group. We plan to recruit into the study for 4 years.**

### **11.2.3 DROP OUT AND DEATH**

Drop out was very low in the previous study but may be higher in an international study. Before the trial stops recruiting, an estimate will be made of drop out by 18 months of age amongst those recruited initially. If drop out and death together exceed 5%, additional infants will be recruited to maintain power.

### **11.3 PROSPECTIVE META-ANALYSIS**

If the opportunity arises, we will collaborate with groups in other countries who undertake a prospectively agreed trial that is identical in all necessary ways to ours within the rules laid down by the Cochrane Collaboration for prospective meta-analyses. This will allow us to collaborate with other countries after our resources, to set up ICISS in those countries, have been exhausted.

## **12. DIRECT ACCESS TO SOURCE DATA AND DOCUMENTS**

Principal investigators will be responsible for the security of data at each local site according to their employing authorities rules and regulations. Only data required for the purposes of the trial will be forwarded to the trial centre. Only members of the TMG and supporting staff will access data at the trial centre.

Permission will be granted to the sponsor's monitors and necessary regulatory authorities for direct access to the data to examine, analyse, verify, and reproduce any records and reports that are important to the evaluation of the clinical trial - subject to them, taking all reasonable precautions to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

## 13. QUALITY CONTROL AND QUALITY ASSURANCE

Quality assurance and quality control systems will be implemented and maintained with written SOPs at the trial centre to ensure that the trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulatory requirements. Principal investigators will be required to comply with the principles of GCP and will be given training if required.

The sponsor will secure agreement from all involved parties to ensure direct access to all trial related sites, source data/documents, and reports for the purpose of validation, monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

### 13.1 MONITORING AND SITE VISITS

Monitoring of data will be undertaken to identify centres that might benefit from a site visit. This is being undertaken by review of CRFs for timeliness, accuracy and obvious errors. Initial contact is then made, as necessary with the investigator by phone or email to try to obtain missing data or to clarify ambiguous data. If this fails to result in adequate data then a site visit will be undertaken. This will be done by a local research nurse (if available) and/or a visit by a member of the TMG or TSC or individuals co-opted with the agreement of the sponsor. Central monitoring by statistical analysis of data from each site is not appropriate in this trial since the number of patients enrolled at each site is relatively small. Similarly, because of the large number of sites (due to the rarity of the condition) it is not practical to consider routine site visits for each site. The purpose of any site visits undertaken is to:

- Confirm that data collected are consistent with adherence to the trial protocol.
- Confirm that accurate assessment of outcome information has occurred.
- Collect any important missing data.

### 13.2 EXTERNAL VERIFICATION

The existence of the patient can be guaranteed by a number of processes. Not all will be available in every patient.

- It is very difficult to fabricate an EEG that is hypersarrhythmic or similar. Thus the EEGs (sent to the trial centre) help to confirm the patient's existence.
- The existence of a consent form for each patient.
- The parent is telephoned by a researcher who thus confirms the existence of a patient of the expected age.
- Similarly other data such as the cranial scan is very difficult to fabricate and again will support the existence of the patient.
- The follow up EEG gives an assessment of response that is blind to treatment allocation.

## 14. ETHICS, R&D AND REGULATORY AUTHORITY APPROVALS

### 14.1 ETHICS APPROVAL

The protocol will be submitted in the UK to the South West MREC for approval and the relevant site specific assessments will then be submitted as required. Similar approvals will be obtained as required in each EU member state and other collaborating countries.

### 14.2 R&D APPROVAL

In the UK, Research & Development (R&D) approval from each participating NHS Trust will be obtained before recruitment can start in that trust. Similar approvals, or letters of approval from the relevant authorities, will be obtained in each EU member state and other collaborating countries.

### 14.3 REGULATORY AUTHORITY APPROVAL

Having obtained a EUDRACT number, a Clinical Trial Authorization (CTA) will be applied for to cover each principal investigator and any other local investigators in the UK. Similar approvals will be obtained for each participating EU member state and other collaborating countries from the relevant regulatory authority.

### 14.4 PRINCIPLES OF GCP

Principal investigators will be asked to sign a statement that will confirm that they understand the principles of Good Clinical Practice as they relate to this trial.

### 14.5 TRIAL MONITORING

The TSC and the sponsor can both request the DMEC to assess the progress of the trial, including safety data and drop out. The DMEC will recommend to the TSC and/or sponsor whether to continue, modify, or stop the trial.

## 15. DATA HANDLING AND RECORD KEEPING

### 15.1 PATIENT IDENTIFICATION

- Each patient enrolled will be assigned a unique ICISS trial identification number. This number will be used in all correspondence between the trial centre and principal investigators.
- A second unique number (which cannot be connected to the ICISS number without access to the protected ICISS database) will be used for all anonymised correspondence (e.g. for the blind EEG assessments).



- Patient identifiable information will be transmitted to the trial centre on only one occasion (consent form). This will be sent by fax. No clinical information will be transmitted at the same time.
- Anonymised data only will be forwarded to the DMEC as required. In cases where the child has died and the entire medical record is to be viewed by the DMEC representative, this anonymisation may not be practical and normal medical record care will apply.

## 15.2 PATIENT RECORDS

- The original signed consent form to participate in the trial will be kept in the patient's medical records unless required otherwise by local regulations.
- The original trial documentation including printed copies of the case report forms (CRFs) will normally be kept in the patient's official medical record once the trial is completed. If kept elsewhere, the trial centre must be notified. The original trial documentation **should not** be forwarded to the trial centre.
- CRFs will be photocopied and sent by post or fax to the trial centre. Only the ICISS number will be used on the CRFs to identify the infant when submitting clinical information.

## 15.3 DATA PROTECTION, SECURITY AND CONFIDENTIALITY

In the UK, data protection, security and confidentiality will be implemented according to the UK Data Protection Act 1998 and each Trust's own Information Governance Policy. At the trial centre, all patient identifiable trial data will be stored in locked filing cabinets when not in use. The trial database will be password-protected and related electronic files will be held on password-protected computers that will be accessed according to Trust policies and procedures. The trial management centre office is locked via a number keypad lock and will be kept locked at all times when the room is unoccupied.

## 15.4 CONTACT TRACING

Due to the time that can pass between enrolment into the trial and subsequent follow up, some infants will have moved house. We will therefore ask each parent or guardian signing the consent form for permission to obtain their new address and telephone number(s) from a third party, such as a grandparent, who is thought unlikely to move. If we lose contact with the parent or guardian, we will ask the third party to tell us where the infant has moved to or to forward to the parent or guardian, our request for their new address and telephone number. Consent to hold this third party contact details will be obtained.

In the UK, the infant's NHS number will be obtained wherever possible to aid contact tracing and permission will be obtained to use this number to contact the parent or guardian. Similar systems in countries outside the UK will be used where available.

## 15.5 ARCHIVING AND STORAGE

Essential clinical trial documents at the trial centre will be stored for 5 years after publication.

## 16. FINANCIAL AND INSURANCE MATTERS

### 16.1 INDEMNITY

The employing authority and the medical and other staff continue to have a duty of care to the patient (and their parent or guardian) whether or not the patient is participating in the trial. Neither the funder nor the sponsor accept liability for negligence on the part of employees of, or staff engaged by other hospitals or health organisations either in the UK or elsewhere and they cannot be held liable for any breach in the duty of care. In the UK, once proper approvals are in place (ethics, R&D, MHRA) the NHS litigation authority will provide to each trust and their employees, indemnity through the negligence scheme for trusts.

Indemnity for negligence will be confirmed in writing as existing before any patient can be recruited in any country outside the UK.

### 16.2 FINANCE

The Chief Investigator is responsible for the management of the funds allocated for the trial in the grant from the Castang Foundation.

As the management of infants in the trial does not involve more than routine good quality care (and since no single hospital will enrol many patients), no funds are allocated to the principal investigators, co-collaborators or their employing authorities for taking part in this trial.

## 17. PUBLICATION POLICY

The results from this trial will be presented at national and international conferences and meetings and will be submitted for publication in medical journals. The Chief Investigator will have the responsibility and authority to submit abstracts for presentation at meetings. It will be the Chief Investigator's responsibility to make the final decision on the draft of any papers to be submitted.

The members of the TSC will be joint authors of any paper reporting main outcomes. National Co-Collaborators and individuals undertaking VABS assessments in each sovereign state outside the UK will also be authors. All enrolling clinicians, principal investigators and regional co-ordinators within countries will be named to allow their involvement to be recognised provided they sign a statement agreeing to be publicly acknowledged within the timeframe required for publication. This list will be submitted to the journal for publication. If this is not agreed by the journal, the list will be made available on the web. The number of patients recruited by enrolling clinicians and those doing the Vineland developmental assessments will be reported. All authors will be asked to sign a statement before publication describing their involvement in conception and design of the project, acquisition, analysis and interpretation of the data and in drafting and revising the paper. If no reply is received from a potential author or someone to be acknowledged, for whatever reason, and the Chief Investigator feels that appropriate attempts to contact them have been made, then the individual will be removed from the list of authors but their contribution will be acknowledged, if allowed by the publisher.

## 18. INFORMATION UPDATES

### 18.1 PARENTAL NEWSLETTER

Parents will be informed of the progress of the trial via a newsletter. This will be produced at the trial centre. It will be translated into the local languages as required for use outside the UK. The newsletter will, wherever possible, be produced once per year and will continue until the final results are submitted for publication. This will enable the results to be sent to the trial participant's parents or guardians (unless they have requested not to receive the newsletters).

In the event of the death of a child, newsletters will not be sent unless the principal investigator reports that the parents or guardians wish to continue to receive the newsletters.

**Principal investigators will be required to inform the trial centre of the death of a child in the study at any age while newsletters continue to be distributed. This will continue until publications from the trial have ceased.**

### 18.2 PRINCIPAL INVESTIGATORS' NEWSLETTERS

Principal investigators will be kept in touch with the trial by means of a newsletter which will be written in English and produced if possible twice per year.

## APPENDIX 1 - PROTOCOL AMENDMENTS

### A1 AMENDMENT P1 (VERSION 1.0 TO VERSION 1.1)

#### A1.1 COVER PAGE

- Additional of ISRCTN Number.
- Amend version number to 1.1.
- Change protocol date to 5<sup>th</sup> April 2006.
- Protocol amendment table updated.
- Version number and date changed in footer (applied to all pages).

#### A1.2 CHAPTER 9 - ADDITION OF 3<sup>RD</sup> BULLET POINT TO SECTION 9.5

- New text is:

*An adjustment will be made for any infant in whom it proved impossible to obtain a Vineland Adaptive Behaviour composite score where a suitable formal developmental assessment undertaken as part of routine care is available.*

#### A1.3 CHAPTER 9 - ADDITION OF NEW SECTION 9.8:

- New text is:

##### 9.8 ASSESSMENT OF UNDERLYING AETIOLOGY

*Underlying aetiology will be classified using the Paediatric adaptation of ICD 10 and grouped as prenatal, perinatal, postnatal, other and not known. Information from the CRFs will be supplemented by direct questions to the study doctor (local treating clinician) as required. Copies of the brain scans will be obtained wherever possible and will be reported by an expert group to maintain consistency in assessment.*

### A2 AMENDMENT P2 (VERSION 1.1 TO VERSION 1.2)

#### A2.1 COVER PAGE

- Date of assignment of ISRCTN, Eudract and Sponsors Protocol numbers added.
- Signature of the Chief Investigator or Principal Investigator text added.
- Amended version number to 1.2.
- Changed protocol date to 19<sup>th</sup> December 2006.
- Protocol amendment table updated.
- Version number and date changed in footer (applied to all pages).

## **A2.1 CHAPTER 1 – GENERAL INFORMATION**

- Website address added – [www.iciss.org.uk](http://www.iciss.org.uk)

## **A2.2 CHAPTER 6 SECTION 6.5 - PRE-RANDOMISATION STRATIFICATION**

Removal of 2 stratification levels:

- Removed original point 2 – Geographical location of the recruiting centre (UK and Ireland, rest of Europe, other).
- Removed original point 4 – Pyridoxine treatment pre-randomisation (yes/no)

## **A2.3 CHAPTER 6 SECTION 6.6 - ALLOCATION OF TREATMENTS**

New text added to Para 2 (shown in italics):

The hormonal treatment will be allocated randomly in the UK and elsewhere this is possible, depending on the availability of both hormonal treatments, parental choice and, *rarely and specified below*, clinical preference. In order to protect recruitment into the trial for the main comparison of combined treatment against hormonal treatment alone, centres and clinicians only willing to take part in the trial if they can choose the hormonal treatment (*clinical preference*) will *only* be allowed to do so if the members of the Trial Steering Committee (TSC) cannot persuade them to randomly allocate the hormonal treatment. *They will not be allowed to take part in the trial if they wish to make this choice for individual patients – only if they wish all patients at their centre to have one of the two hormonal treatments.* Parents will always be allowed to choose the hormonal treatment if they do not wish it to be randomly allocated

## **A2.4 CHAPTER 7 SECTION 7.2 - EXCLUSION CRITERIA**

Text added to Bullet Point 5 (shown in italics):

- Previous treatment for Infantile Spasms other than a therapeutic trial of pyridoxine to exclude pyridoxine dependent seizures (*see Section 8.2*).

## **A2.5 CHAPTER 8 SECTION 8.1 - TIME BETWEEN DIAGNOSIS AND TREATMENT ALLOCATION**

Text added (shown in italics):

Infants should be enrolled into the trial as soon as possible but sufficient time must be given to the parents/guardians to allow them to read the information about Infantile Spasms and the trial before consent is obtained. *See also exclusions, Section 7.2.*

## **A2.6 CHAPTER 8 SECTION 8.2 - TREATMENT WITH PYRIDOXINE BEFORE ALLOCATION OF A RANDOMISED TREATMENT**

Text added (shown in italics):

The possibility of pyridoxine dependent seizures may be considered before offering a trial treatment. **We suggest** that *a therapeutic trial for pyridoxine dependent seizures* is only necessary in those infants:

- with additional seizure types, **and**
- where no other cause for their spasms is known.

*Please note the child is excluded from entry to the trial if pyridoxine is given as a treatment for infantile spasms when you are **not** considering the diagnosis of pyridoxine dependent seizures (Section 7.2).*

## **A2.7 CHAPTER 9 SECTION 9.2.1 - PRIMARY LATE OUTCOME: DEVELOPMENT AT 18 MONTHS**

Final sentence of Para 2 deleted and text added (shown in italics):

The Vineland has four domains (communication, daily living skills, socialization and motor skills) and these can be combined to give an Adaptive Behaviour Composite (ABC) score. The ABC score has a standard score of 100 and a standard deviation of 15. The group means (or medians if not normally distributed) for the ABC score and domain scores will be compared for each treatment group for all infants by intention to treat. *We will also investigate to see if there is an interaction between treatment and aetiology (see Section 5.3 for the definition of no identified aetiology).*

## **A2.8 CHAPTER 9 SECTION 9.5 - SENSITIVITY ANALYSES**

Bullet Point 4 added (shown in italics):

- *An adjustment will be made for infants lost to developmental follow up.*

## **A2.9 CHAPTER 9 SECTION 9.8 - ASSESSMENT OF UNDERLYING AETIOLOGY**

Text added to Para 1 (shown in italics):

Underlying aetiology will be classified using the Paediatric adaptation of ICD 10 and grouped as prenatal, perinatal, postnatal, other and not known. Information from the CRFs will be supplemented by direct questions to the study doctor (local treating clinician) as required. Copies of the brain scans will be obtained wherever possible and will be reported by an expert group to maintain consistency in assessment (*see also Section 5.3, Definitions*).

## **A2.10 CHAPTER 11 SECTION 11.1 - STATISTICAL METHODS**

Bullet Point 7 amended from:

- All deaths will be reported. Infants lost to follow up will be reported and sensitivity analyses undertaken if appropriate

To read:

- *All deaths and all infants lost to follow up will be reported.*

Text added after Bullet Point 7 (shown in italics):

*Specifically, we intend to examine for any interaction between treatment and aetiology. Post-stratification analyses will be undertaken to see what effect, if any, the following may have had on the main outcomes:*

- 1 Use of pyridoxine*
- 2 English as the language used for the Vineland assessments.*

## **A2.11 CHAPTER 11 SECTION 11.2.2 - MAIN LATE OUTCOME: DEVELOPMENT**

Text added to Para 2 (shown in italics):

The difference in development in UKISS was found only in the subgroup with no identified aetiology. In this group, the VABS score was 88 for those on hormonal treatment alone and will need to improve to 95 on both treatments to be of clinical importance. The power to detect this difference is 90% with 85 infants with no cause found in each group, using two sided tests. 85 infants with no cause found will be found within 205 infants in each treatment group. We are likely to see a bigger difference in development between the two groups at 18 months than UKISS found at 14 months. *205 infants in each group will give us 99.75% power to detect a difference of half a standard deviation in the main late outcome comparing the two treatment groups (VABS score increasing from 78.6 (SD 16.8) to 86.1 (SD 15).*

## **A3 AMENDMENT P3 (VERSION 1.2 TO VERSION 1.3)**

### **A3.1 COVER PAGE**

- Amended version number to 1.3.
- Changed protocol date to 5<sup>th</sup> January 2011.
- Removed text ‘Protocol Approved by: South West MREC on:’
- Protocol amendment table updated – row 2 replaced with text ‘Protocol Date’. Rows 3 & 4 deleted.
- Version number and date changed and page X of Y updated in footer (applied to all pages).

### **A3.2 CHAPTER 1 – GENERAL INFORMATION**

- Name and address for Chief Investigator, Trial Manager and Deputy Chief Investigator removed from this section
- Name of Sponsor’s Representative removed from this section.

These changes were made to avoid having to amend the protocol if any changes to trial personnel occurred in the future.

### **A3.3 CHAPTER 7 SECTION 7.2 – EXCLUSION CRITERIA**

The first **two** exclusions have been amalgamated to the following:

- *More than 7 days has elapsed since the diagnosis was made through the combination of the EEG result and confirmation of the clinical features by the consultant in charge or his/her nominated deputy.*

This change reflects two facts:

1. A change in practice, with the majority of clinicians no longer considering that they can make a diagnosis before the EEG result is known.
2. It is also possible to allow 7 days to elapse following confirmation of the diagnosis now that data from UKISS has given us an insight into the effect of any such delay (paper submitted for publication).

We remain committed to encouraging clinicians not to delay before starting treatment for infantile spasms. Section 8.1 still states that infants should be enrolled into the trial as soon as possible but sufficient time must be given to the parents/guardians to allow them to read the information about Infantile Spasms and the trial before consent is obtained.

#### **A3.4 CHAPTER 8 SECTION 8.4.2 - HORMONAL TREATMENT (PREDNISOLONE OR TETRACOSACTIDE DEPOT) ROUTE AND DOSE**

The heading has been changed to the above by the addition of the words in brackets to make it clear in this section, as it is elsewhere in the document, that hormonal treatment is either prednisolone or tetracosactide depot.

#### **A3.5 CHAPTER 8 SECTION 8.5 - TREATMENT AFTER DAY 14 IN THOSE WITH NO SPASMS ON AND BETWEEN DAYS 14 AND 42 INCLUSIVE.**

This heading has been changed to the above by the addition of the words in italics, to remind investigators that treatment after Day 14 is only mandated in those who are potential responders.

#### **A3.6 CHAPTER 8 SECTION 8.5.2 - VIGABATRIN TREATMENT IN THOSE ALLOCATED COMBINED TREATMENT (BOTH VIGABATRIN AND HORMONAL)**

This section has had “*potential responders*” added to remind investigators that treatment is not mandated by the protocol in non-responders, although this should be clear from the title of Section 8.5. The first paragraph of Section 8.5.2 now begins “Those *potential responders* allocated...”.

#### **A3.7 CHAPTER 8 SECTION 8.9 - DRUG ACCOUNTABILITY**

The heading has been changed to the above.

##### **Drug accountability**

It has not proved possible to validate whether we are being accurately reported by the investigator that the patient had dosing errors within 20% or if a whole day goes by without the recommended increase as per protocol. In retrospect, we realise that this definition was too specific and unnecessary. We therefore suggest this change to the protocol to reflect what is possible and sufficient for this trial.



The treatment is specified in Section 8.4 in detail since we would like investigators and parents to follow the treatment schedule wherever possible. However, this is a pragmatic trial and we accept that variations to the treatment schedule will often be in the best interest of the child for many reasons including but not limited to the age of the child (affecting, for example, sleep routine or feeding routine) or the effect of other medical or social conditions that many of the infants will also have. Family circumstances can also have an effect.

We do not believe that missing a single dose or delaying an expected increase by less than 24 hours would result in a measurable effect on our outcome measures. Thus, we had chosen our definition “We will report failure to increase the dose at the expected time if a whole day or more goes by before the appropriate increase is made. Dosing errors greater than 20% will be reported” (Protocol Section 8.9) and this was intended to collect a single missing dose or a significant delay in increasing a dose.

We also do not wish to interfere with the normal relationship between the parents and the doctor – we wish to have minimal impact on clinical practice. We do not believe in diary records of treatment given believing that these have been discredited in epilepsy (and diabetes) but prefer to rely on the open relationship between the parents and the investigator. This allows clarification with the parent that they should take the treatment as intended but that, if they do not, they should tell us without fear of recrimination.

Thus we monitor drug accountability only by direct questioning of the parents/carer by the investigator – asking the question in a CRF, “Was the allocated treatment given accurately according to the protocol” The response to this single question is intended to capture whether the treatment was both prescribed and administered accurately.

Section 8.9 now reads:

*We are monitoring drug accountability by direct questioning only. As this is a pragmatic trial, some dosage errors are expected which are not believed to have a measurable effect on our outcome measures. Investigators will report, at the Day 15 and Day 43 assessments, the answer to the question “Was the allocated treatment given accurately according to the protocol?”. The response to this question will be based on direct communication between the investigator and the parent/carer.*

### **A3.8 CHAPTER 10 SECTION 10.3 – DURATION OF ADVERSE REACTION REPORTING**

We have removed the unnecessary reference to adverse events in section 10.3, for clarity.

### **A3.9 CHAPTER 10 SECTION 10.5 - ADVERSE REACTIONS SPECIFIC TO THE MEDICINES USED IN THIS TRIAL**

We also realise that our list of expected reactions could be increased without affecting the safety of patients by allowing reactions to be expected if they are known and thus are listed in the summary of product characteristics (SpC) used as our Investigators’ Brochure. We have therefore changed the wording in section 10.5 to:

*“Adverse reactions are known to be associated with the trial treatments. The reactions listed below, and any others documented in the IMP dossier, will be the expected adverse reactions and will not be reported as SUSARs.”*

### **A3.10 CHAPTER 11 SECTION 11.3 - PROSPECTIVE META-ANALYSIS**

We have added this new section, 11.3 to state:

*If the opportunity arises, we will collaborate with groups in other countries who undertake a prospectively agreed trial that is identical in all necessary ways to ours within the rules laid down by the Cochrane Collaboration for prospective meta-analyses. This will allow us to collaborate with other countries after our resources, to set up ICISS in those countries, have been exhausted.*

This may allow us to reduce the number of infants needed in ICISS and thus shorten the time to the end of the trial. It does not commit us to any such collaboration.

### **A3.11 CHAPTER 13 SECTION 13.1 - MONITORING AND SITE VISITS**

Section 13.1 has been expanded and re-written and now states:

*Monitoring of data will be undertaken to identify centres that might benefit from a site visit. This is being undertaken by review of CRFs for timeliness, accuracy and obvious errors. Initial contact is then made, as necessary with the investigator by phone or email to try to obtain missing data or to clarify ambiguous data. If this fails to result in adequate data then a site visit will be undertaken. This will be done by a local research nurse (if available) and/or a visit by a member of the TMG or TSC or individuals co-opted with the agreement of the sponsor. Central monitoring by statistical analysis of data from each site is not appropriate in this trial since the number of patients enrolled at each site is relatively small. Similarly, because of the large number of sites (due to the rarity of the condition) it is not practical to consider routine site visits for each site. The purpose of any site visits undertaken is to:*

- *Confirm that data collected are consistent with adherence to the trial protocol.*
- *Confirm that accurate assessment of outcome information has occurred.*
- *Collect any important missing data*

### **A3.12 CHAPTER 13 SECTION 13.2 – EXTERNAL VERIFICATION**

It has not proved possible to obtain the support of third parties at each site to undertake external verification. This section has been rewritten as follows:

*The existence of the patient can be guaranteed by a number of processes. Not all will be available in every patient.*

- *It is very difficult to fabricate an EEG that is hypersarrhythmic or similar. Thus the EEGs (sent to the trial centre) help to confirm the patient’s existence.*
- *The existence of a consent form for each patient.*

- *The parent is telephoned by a researcher who thus confirms the existence of a patient of the expected age (at 18 months).*
- *Similarly other data such as the cranial scan is very difficult to fabricate and again will support the existence of the patient.*
- *The follow up EEG gives an assessment of response that is blind to treatment allocation.*

### **A3.13 CHAPTER 15 SECTION 15.2 - PATIENT RECORDS**

Electronic case report forms are not being used. We have therefore removed reference to them. The final bullet point of this section now reads:

- *CRFs will be photocopied and sent by post or fax to the trial centre. Only the ICISS number will be used on the CRFs to identify the infant when submitting clinical information.*