MENDS: The use of MElatonin in children with Neuro-developmental Disorders and impaired Sleep; a randomised, double-blind, placebo-controlled, parallel study

Version 7.0, 01/04/10

Identifying Numbers: HTA 05/14/02 / Eudract 2006-004025-28 / ISRCTN05534585/MREC 07/MRE08/43

Authorised on behalf of the Sponsor:

Signed: M. Paul Date: 07.04.10

Name DR MATTHEW PERRY

Title DIRECTOR OF RESEARCH

General Information

This document describes the MENDS trial and provides information about procedures for entering patients into it. The protocol should not be used as an aide-memoir or guide for the treatment of other patients. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to the registered investigators in the trial, but centres entering patients for the first time are advised to contact the coordinating centre (Medicines for Children Research Network Clinical Trials Unit (MCRN CTU), University of Liverpool, (mends@mcrnctu.org.uk, 0151 282 4523) to confirm they have the most up to date version. Clinical problems relating to this trial should be referred to the relevant Chief Investigator via the MCRN CTU.

Statement of Compliance

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

Contact Details: Institutions

Funder:	Sponsor:	Trial Management and Monitoring:
NHS R&D National Coordinating Centre for Health Technology Assessment Mailpoint 728, Bolderwood, University of Southampton, Southampton SO16 7PX	Dr Matthew Peak Director of Research Alder Hey Children's NHS Foundation Trust Alder Hey Eaton Road, Liverpool, L12 2AP	Medicines for Children Clinical Trials Unit Institute of Child Health Alder Hey Children's NHS Foundation Trust Liverpool L12 2AP
Central Laboratory Facility (salivary melatonin assay):	**Central Laboratory Facility (laboratory analysis of DNA):**	**Clinical Trial Supplies**
Professor Debra Skene Professor of Neuroendocrinology School of Biomedical and Molecular Sciences University of Surrey Guildford GU2 7XH	Thomas Bourgeron Génétique humaine et fonctions cognitives Human Genetics and Cognitive Functions Institut Pasteur 25 rue du Docteur Roux 75724 Paris CEDEX 15 France	Penn Pharmaceutical Services Limited Tredegar Gwent NP22 3AA Alliance Pharmaceuticals Ltd Avonbridge House Bath Road Chippenham Wilts SN15 2BB

DETAILS OF PARTICIPATING SITES ENTERED IN APPENDIX A

Contact Details: Individuals

Individual Authorised to Sign the Protocol and Protocol Amendments on behalf of the Sponsor:	**Chief Investigator (CI):**	**Lead Investigator (Northern Centres):**
Dr Matthew Peak Director of Research Alder Hey Children's NHS Foundation Trust Eaton Road, Liverpool, L12 2AP	Dr Richard Appleton Consultant Paediatric Neurologist The Roald Dahl EEG Department Paediatric Neurosciences Foundation Alder Hey Hospital Eaton Road, Liverpool, L12 2AP Tel: 0151 252 5851 Fax: 0151 252 5152 E-mail: Richard.Appleton@alderhey.nhs.uk	Dr Richard Appleton Consultant Paediatric Neurologist The Roald Dahl EEG Department Paediatric Neurosciences Foundation Alder Hey Hospital Eaton Road, Liverpool, L12 2AP Tel: 0151 252 5851 Fax: 0151 252 5152 E-mail: Richard.Appleton@alderhey.nhs.uk
Lead Investigator (Southern Centres):	**Medical Expert who will Advise on Protocol Related Clinical Queries and Evaluate SAE Reports (in absence of Co-lead Investigators):**	**Trial Co-ordinator:**
Dr Paul Gringras Consultant in Paediatric Neurodisability Evelina Childrens Hospital St Thomas' Hospital Lambeth Palace Road, London, SE1 7EH	Dr A G Sutcliffe Senior lecturer in child health University College London Institute of Child Health 1st Floor West 250 Euston Road London, NW1 2PQ	Miss Charlotte Stockton Medicines for Children Clinical Trials Unit Institute of Child Health Alder Hey Children's NHS Foundation Trust Liverpool L12 2AP
Statistics Team Leader:	**Trial Statistician:**	
Dr Carrol Gamble Reader in Medical Statistics Medicines for Children Clinical Trials Unit Institute of Child Health Alder Hey Children's NHS Foundation Trust Liverpool L12 2AP	Mr Ashley Jones Senior Statistician Medicines for Children Clinical Trials Unit Institute of Child Health Alder Hey Children's NHS Foundation Trust Liverpool L12 2AP	

Independent Oversight Committees

Data Monitoring Committee		
Professor David R Jones Professor of Medical Statistics Adrian Building Room 218 University of Leicester University Road Leicester LE1 7RH	Dr John Gibbs Consultant Paediatrician Paediatric Department, Countess of Chester Hospital, Liverpool Road, Chester CH2 1UL	Prof A G Marson (Chairperson) Professor of Neurology Division of Neurological Science University of Liverpool Clinical Sciences Centre Lower Lane Fazakerley Liverpool L9 7LJ

Independent members of the Trial Steering Committee*		
Professor Stuart Logan (Chairperson) Professor of Paediatric Epidemiology Director - Institute of Health and Social Care Research Peninsula Medical School St Luke's Campus Heavitree Road Exeter EX1 2LU Email: stuart.logan@pms.ac.uk Secretary: Stella Taylor	Mr Andy Vail R&D Support Unit Clinical Sciences Building Hope Hospital Stott Lane Salford M6 8HD	Dr Michael Anthony McShane Consultant Paediatric Neurologist John Radcliffe Hospital Headley Way Headington Oxford OX3 9DU

* Non-independent members listed in section 16.

Table of Contents

List of abbreviations

ABAS	Adaptive Behaviour Assessment System
ABC	Aberrant Behaviour Checklist
ADR	Adverse Drug Reaction
AE	Adverse Event
CI	Chief Investigator
CRF	Case Report Form
CSHQ	Children's Sleep Habits Questionnaire
CTU	Clinical Trials Unit (refers to MCRN CTU)
DMEC	Data Monitoring and Ethics Committee
DNA	Deoxyribonucleic Acid
eCRF	Electronic Case Report Form
GMP	Good Manufacturing Practice
GP	General Practitioner
IB	Investigator's Brochure
DMC	Data Monitoring Committee
IEC	Independent Ethical Committee
IMP	Investigational Medicinal Product
LREC	Local Research Ethics Committee
MCRN CTU	Medicines for Children Clinical Trials Unit
MREC	Multi-centre Research Ethics Committee
NPSA	National Patient Safety Agency
PI	Principal Investigator
PIC	Patient Information and Consent form
R&D	Research & Development
RP	Research Practitioner
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SCQ	Social Communication Questionnaire
SNP	Single Nucleotide Polymorphism
SPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TESS	Treatment Emergent Signs and Symptoms
TMF	Trial Master File
TSC	Trial Steering Committee
UAR	Unexpected Adverse Reaction

1 PROTOCOL SUMMARY

Title: The use of MElatonin in children with Neuro-developmental Disorders and impaired Sleep; a randomised, double-blind, placebo-controlled, parallel study.

Phase: II

Population: 114 children aged 3 years to 15 years 9 months, at randomisation, with a diagnosis of a neuro-developmental disorder in conjunction with a minimum six month history of impaired sleep as defined by not falling asleep within one hour of 'lights off' or 'snuggling down to sleep' at age-appropriate times for the child in 3 nights out of 5, and/or less than 6 hours of continuous sleep in 3 nights out of 5.

Number of Sites: Twenty five sites throughout England; see Appendix A for full details.

Study Duration: Potential participants will be screened and initially registered on study at T-4 Weeks. The family will be given a standardised booklet on basic sleep hygiene but no other intervention (behavioural, pharmacological or homeopathic) to try and improve their child's sleep. Sleep diaries and an actigraph will be provided with instructions for use and will be used for the duration of the 4 week sleep hygiene intervention. Contact will be re-initiated at T-2 weeks to check the sleep diaries and the actigraphy data and to stress the importance of a consistent bedtime. At the end of 4 weeks (T0), assuming the child continues to fulfil the entry criteria and further consent is provided; the child will be randomised into the study. Each child will be followed up for 12 weeks from date of randomisation, by a combination of home visits, telephone contact and clinic attendance.

Description of Intervention: The active compound (melatonin) and placebo (matching in package and appearance) will be administered 45 minutes prior to the child's usual bedtime; wherever possible, this time will remain the same throughout the study. The starting dose will be 0.5 mg and will increase every 7 days through 2mg and 6 mg up to a maximum of 12 mg, depending upon the patient's response to the preceding dose. The study treatment will be administered orally or, if the patient is not able to feed orally, through a nasogastric feeding tube or gastrostomy feeding tube; in these latter two situations the capsule will be opened and the study treatment suspended in an appropriate vehicle for administration.

Primary Outcome:

Total night-time sleep calculated using sleep diaries

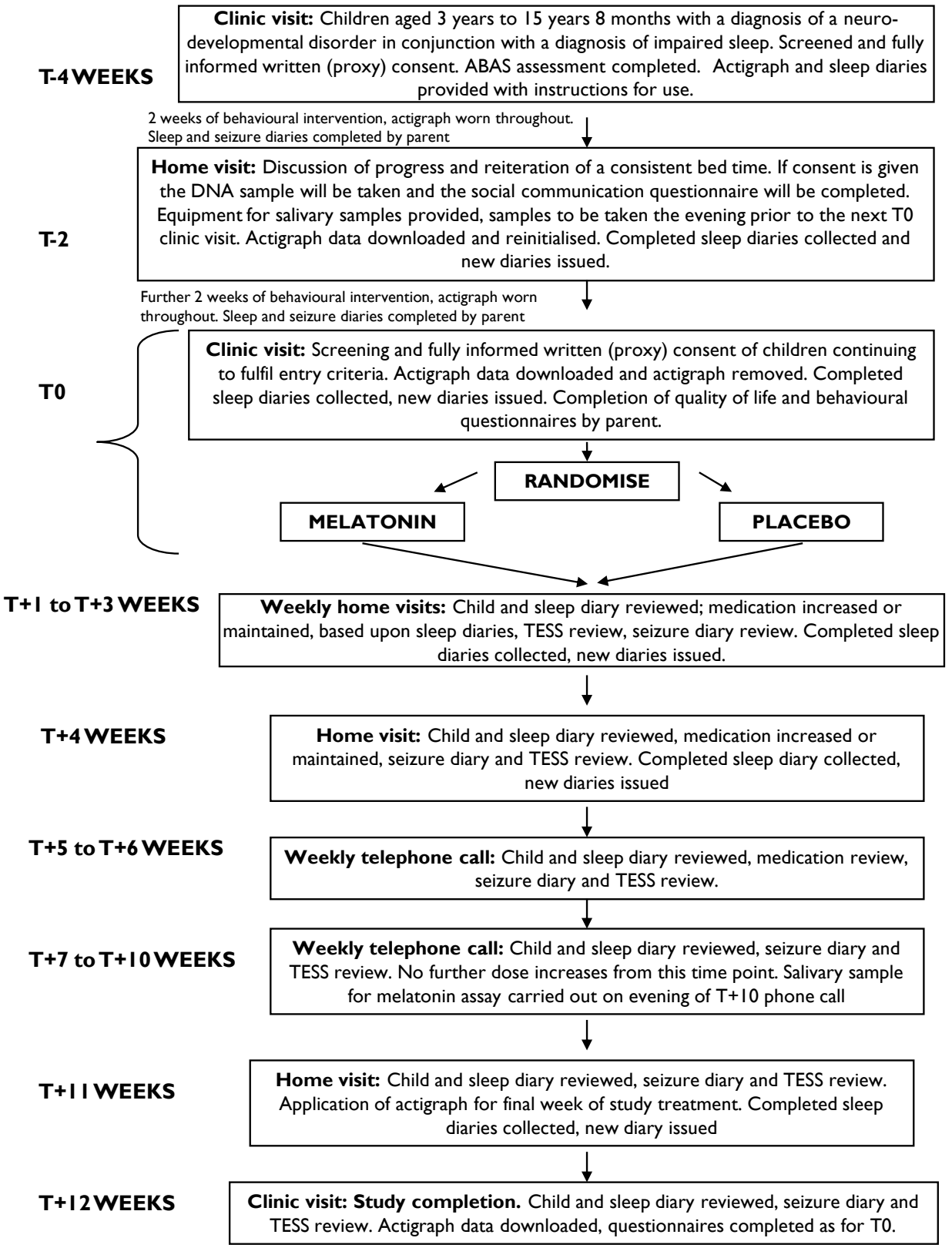
Secondary Outcomes:

1. Total night time sleep calculated using actigraphy data
2. Sleep onset latency (the time taken to fall asleep) calculated using actigraphy data
3. Sleep onset latency (the time taken to fall asleep) calculated using sleep diaries
4. Assessment of effects on (a) cognitive function; (b) behavioural problems; (c) epilepsy; (d) quality of life; (e) sleep efficiency and behaviour (f) salivary melatonin

concentrations and (g) association of genetic variants with abnormal melatonin production.

5. Adverse effects

Protocol Summary – continued
Fig 1. Schematic of Study Design:



2 BACKGROUND INFORMATION

2.1 Introduction

Melatonin (N-acetyl-5-methoxytryptamine) is a natural substance produced by the pineal gland and is responsible for circadian rhythm producing sleep. Production of melatonin is increased in the evening and suppressed by light, making melatonin a hormonal signal of darkness. In mammals (including humans), melatonin regulates the circadian rhythm (including sleep-wake cycling). Considerable work undertaken in healthy adult volunteers has evaluated the pharmacology and pharmacokinetics of both endogenous and prescribed exogenous melatonin. Early results (subsequently confirmed) suggested that melatonin is of value in treating sleep disturbances in blind or severely visually-impaired people in whom endogenous melatonin secretion may be altered or deficient. Melatonin has also been suggested to be useful in inducing sleep in groups at specific risk of insomnia including shift-workers[1] and those with jet lag[2].

Children with neurological and/or developmental disorders have a higher prevalence of sleep disturbances that are frequently chronic and are usually far more difficult to treat than their 'normally' developing peers[3-5]. These sleep disorders may result in additional learning and behaviour problems. In addition, disturbed sleep, and specifically discontinuous sleep with frequent awakenings throughout the night, commonly results in disturbed sleep in their parents and siblings with secondary detrimental effects on the family – physically, emotionally and socially – and if chronic, even on their ability to continue in employment or further education. Finally, chronic sleep disturbance of multiply disabled children are a frequent cause of families giving up their care.

Behavioural approaches used in improving sleep are difficult to apply, time-consuming and usually require skilled and scarce manpower. Treatment with commonly-used hypnotic sedative drugs is often ineffective and can result in both side effects and tolerance, and may even be contraindicated in certain situations. There is considerable evidence that chronic sleep-wake disorders of children with neuro-developmental disorders are associated with an inability to synchronise their sleep-wake cycle generating system with environmental zeitgebers, resulting in abnormal melatonin secretion[6-8]. Following early results suggesting that melatonin may be effective in improving sleep in these children[3;8], together with the observation that melatonin appeared to have neither short- nor long-term side-effects, melatonin was (and continues to be) increasingly used in open studies in the treatment of sleep disorders of children with a range of neurological disabilities and disorders. Furthermore, in view of the fact that children with a range of neuro-developmental disorders will be seen by many different disciplines and specialists including general (hospital and community-based) paediatricians, paediatric neurologists and child and adolescent psychiatrists, there has been a predictable enthusiasm to find an intervention or drug that is both effective and 'safe' in treating the sleep impairment that is typically seen in these children. This would, at least in part, explain the dramatic increase in the prescription of melatonin for this population throughout the UK.

2.2 Rationale

Several studies have suggested that melatonin is beneficial in children with developmental delay and in particular those with visual problems[3;9-11] but also in more specific neuro-genetic syndromes, including Rett syndrome[12] and tuberous sclerosis[13]. Importantly, melatonin appears to be effective in both reducing the time it takes children to fall asleep (time to sleep onset or sleep latency) as well as increasing the total duration of continuous sleep throughout the night[3;10;14;15]. However, all of these studies have been non-randomised and anecdotal. Limited controlled clinical trial data have suggested that melatonin may significantly reduce the time to fall asleep (i.e.: reduced sleep latency) with a definite (but

statistically non-significant) increase in total sleep duration[16-19]. Recent placebo-controlled trials have demonstrated that melatonin appears to be effective in elementary (primary) school children without neuro-developmental delay or neurological disorders and idiopathic chronic sleep onset insomnia[18;19] as well as in some children with epilepsy[20;21]. The drug has also been used with some success in inducing sleep in children undergoing a range of medical procedures, including sedation electroencephalograms (EEGs) and even brain scans[22;23]

Melatonin levels in both saliva and blood vary from person to person for a number of reasons, some known, some unknown; these may include the person's age and any underlying neurological or visual impairment. Consequently, neither therapeutic levels nor physiological, nor pharmacological doses have been established. There is some evidence that there may be a dose-response relationship for both melatonin[24-26] and melatonin agonists (β-Methyl-6-Chlormelatonin)[27]. Finally, there is no convincing evidence that tolerance develops to exogenous melatonin[9;11] and there is considerable anecdotal evidence, from practising clinicians that, in many children, once their sleep pattern has 'improved' the melatonin can even be discontinued without a relapse in the sleep disturbance.

Melatonin is considered to be a safe drug with no reported serious adverse side-effects; hypothermia, asymptomatic hypotension, drowsiness, a 'hung-over' effect and occasional headaches have been inconsistently reported from a number of anecdotal studies. One study has suggested that seizure control may deteriorate in some children with epilepsy[28] but this observation has not been confirmed in subsequent anecdotal and limited randomised controlled studies[11;20;21]; there is some anecdotal evidence that seizure control may actually improve as a secondary effect of improved sleep and increased seizure-threshold[3].

The drug is unlicensed for this clinical use (of improving sleep in children whether or not the child has neuro-developmental problems) and it is estimated that in the UK there are currently well in excess of 5000 children being treated with melatonin. In some countries, including the USA, melatonin is considered to be a food supplement and not subject to the regulations governing medicinal agents. Finally, there are at least 50 preparations that are either being imported into, or manufactured within, the UK, including immediate release capsules and tablets, sustained-release capsules and tablets and at least one liquid formulation. The majority of these formulations are health foods/ dietary supplements with no guarantee of quality or preparations manufactured to the standards of Good Manufacturing Practice (GMP).

Current, and predominantly anecdotal evidence, together with the rapidly increasing and largely haphazard use of melatonin, clearly justifies the need to undertake a multi-centre, randomised, placebo-controlled parallel study of melatonin in children with a range of neuro-developmental delay / neurological disorders and impaired sleep to confirm (or refute) the findings that the drug may reduce the time taken to fall asleep and increase the total duration of night-time sleep.

2.3 Objective

The objective of this trial is to confirm (or refute) that immediate release melatonin is beneficial compared to placebo in improving total duration of night-time sleep in children with neuro-developmental problems.
At randomisation, each patient will be allocated their own 'individual patient package' (stored in pharmacy and dispensed according to Section 7.4) containing either melatonin or placebo. Each child will be given the first dose and kept on that dose for a minimum of seven days. For the next three weeks and at each one-week interval during this time, the child's sleep disorder will be reviewed and the medication either left unchanged or increased to the next

dose increment. There are a maximum of 3 dose increments after the starting dose of 0.5 mg, through 2, 6 and up to a maximum of 12 mg (Section 7.9). Each child will remain on whichever dose is felt to have been the most effective.

2.4 Potential Risks and Benefits

2.4.1 Potential Risks

Clinical studies in humans (adult volunteers and patients of both sexes and all ages) have not shown any consistent or serious short or long-term adverse side-effects[29]. Most of the reported adverse side-effects have been described in very small numbers of patients[16;30]. Although the chronic use of exogenous melatonin for sleep problems in paediatrics appears widespread, there is a paucity of data on its safety. Melatonin is widely distributed at different densities throughout the body and appears to be implicated in various physiological functions other than sleep. There are therefore theoretical risks in the chronic administration of exogenous melatonin in this patient population. The most significant theoretical risks in this population are:

- sexual development
- nocturnal asthma
- growth
- seizures.

With age, nocturnal melatonin levels appear to decrease with the most striking falls appearing to occur around puberty. Nocturnal melatonin levels have been assessed in children at various pubertal stages and it is observed that they are higher in the earlier than in the later stages[31]. Whether this is cause or effect is not known but there is a potential risk that exogenous melatonin may delay sexual maturity.

Elevated endogenous melatonin levels have been associated with an increased incidence of nocturnal asthma[32] although there is at least one study in adults that demonstrated an improvement in sleep in adults with asthma following administration of 3mg melatonin with no apparent worsening of their asthma symptoms[33].

Melatonin has been observed to have a direct effect on growth hormone[34]. Eight male volunteers received single doses of 0.05, 0.5 and 5mg melatonin or placebo with serum growth hormone levels measured for up to 150 minutes afterwards. Compared with placebo, growth hormone levels were found to increase for doses of 0.5 and 5mg. The exact mechanism is not clear and the effect of increases in growth hormone of this magnitude on longitudinal bone growth in children is not known.

One study has suggested that seizure control may deteriorate in some children with epilepsy[28] but this observation has not been confirmed in subsequent anecdotal and limited randomised controlled studies[20;35]; there is some anecdotal evidence that seizure control may actually improve as a secondary effect of improved sleep and increased seizure-threshold[3]. There have been two spontaneous reports to the MHRA of seizures associated with exogenous melatonin and responders to the survey by Waldron et al[30] reported an increase in seizure activity or new onset seizures.

Melatonin oral capsules contain melatonin, lactose, and magnesium stearate. Placebo oral capsules contain lactose and magnesium stearate. Individuals with lactose intolerance are able to consume significant quantities of dairy products without displaying any symptoms of lactose malabsorption, therefore individuals with lactose intolerance will be eligible for inclusion.

2.4.2 Known Potential Benefits

Very few meta-analyses[16;29] of randomised controlled trials (RCT) exist, those that have been undertaken indicate that exogenous melatonin may improve sleep in a number of clinical situations including:

- children with neurological and psychiatric disorders
- patients with visual impairment (particularly where the visual impairment is due to an abnormality within the anterior visual pathway [specifically in patients with microphthalmia or anophthalmia] rather than in cortical visual impairment)
- elderly patients with insomnia.

Reported benefits include a reduced sleep latency time (ie: reduced time to fall asleep), reduced number of awakenings throughout the night (ie: increased periods of continuous, un-interrupted sleep throughout the night) and improved behaviour and performance during the day.

However, the reported studies have marked heterogeneity of inclusion and exclusion criteria, the type and causes of impaired sleep in the populations studied, the doses and formulations of melatonin used, methods of assessment, and reported outcomes.

3 SELECTION OF CENTRES/CLINICIANS

Each participating Centre (and investigator) has been identified on the basis of:

- being responsible for a large population of children with neuro-developmental problems
- having at least one lead clinician with a specific interest in, and responsibility for, supervising and managing children with a wide range of neuro-developmental and neurological disorders
- having had experience with prescribing melatonin
- showing enthusiasm to participate in the study
- ensuring that sufficient time, staff and adequate facilities are available for the trial
- providing information to all supporting staff members involved with the trial or with other elements of the patient's management
- identifying that they will be able to recruit a specified target number of patients (see section 9)
- acknowledging and agreeing to conform to the administrative and ethical requirements and responsibilities of the study, including signing-up to Good Clinical Practice and other regulatory documentation.

3.1 Centre/Clinician Inclusion Criteria

a. Positive Site Specific Assessment by LREC
b. Local R&D approval
c. Receipt of evidence of completion of (a) and (b) by MCRN CTU
d. Completion and return of 'Signature and Delegation Log' to MCRN CTU
e. A speciality interest in, and clinical responsibility for, caring for children and young people with neuro-disability and neurological or neuro-developmental disorders.

3.2 Centre/Clinician Exclusion Criteria

a. Not meeting the inclusion criteria listed above.

4 TRIAL DESIGN

4.1 Primary Outcome

1. Total duration of night-time sleep calculated using the sleep diary.

4.2 Secondary Outcomes

1. Total night time sleep calculated using actigraphy data
2. Sleep efficiency calculated from the actigraphy by (number of minutes spent sleeping in bed/total number of minutes spent in bed) x 100
3. Sleep onset latency (the time taken to fall asleep) calculated using actigraphy
4. Sleep onset latency (the time taken to fall asleep) calculated using sleep diaries
5. Composite sleep disturbance index scores
6. Daily global measure of parental perception of child's sleep quality
7. Behavioural problems assessed using Aberrant Behaviour Checklist (ABC)
8. Quality of Life of the care-giver assessed using the Family Impact Module of the PedsQL ™
9. Level of daytime sleepiness of caregiver assessed using the Epworth Sleepiness Scale
10. Number and severity of seizures evaluated using seizure diaries throughout trial follow-up
11. Adverse effects of melatonin treatment assessed weekly between weeks T0W to T12W using 'TESS' (Treatment Emergent Signs and Symptoms) (Section 8.4.1)
12. Salivary melatonin concentrations
13. Associations between genetic variants and abnormal melatonin production

5 STUDY POPULATION

5.1 Inclusion Criteria

1. Children aged 3 years to 15 years 8 months at screening.
2. Diagnosis of a neuro-developmental disorder that has been made by a community paediatrician, paediatric neurologist or paediatric neurodisability consultant, categorised as:
    a. developmental delay alone
    b. developmental delay and epilepsy*
    c. developmental delay and autistic spectrum disorder* (ASD)
    d. developmental delay with 'other' ('other' is defined as the child having a specific genetic/chromosomal disorder).

    or any combination of the above.
3. Adaptive Behaviour Assessment System (ABAS) questionnaire score with a percentile rank below 7.
4. Minimum 5 months history of impaired sleep at screening as defined by:
    a. not falling asleep within one hour of 'lights off' or 'snuggling down to sleep' at age-appropriate times for the child**, and/or:
    b. less than 6 hours of continuous sleep in three nights out of five
5. Children whose parents are likely to be able to use the actigraph and complete sleep diaries
6. Children who are able to comply with taking the study drug
7. English speaking
8. Children whose parents have completed sleep diaries for an average of 5 out of 7 nights at T0W.

* In coding the presence of epilepsy and ASD diagnoses, we will require sight of documentation from relevant services that demonstrate appropriate diagnostic assessments and investigations have been used

** This will be the child's usual bedtime (recorded in the sleep diary) based upon the family's normal routine

5.2 Exclusion Criteria

1. Children treated with melatonin within 5 months prior to screening
2. Children who have been taking the following medication for less than 2 months:
    - any benzodiazepines
    - amisulpride (Solian)
    - chlorpromazine (Largactil)
    - haloperidol (Haldol)
    - olanzapine (Zyprexa)
    - risperidone (Risperdal)
    - sertindole (Serdolect)
    - sulpiride (Sulpidil, Sulpor)
    - thioridazine (Melleril)
    - trifluoperazine (Stelazine)
3. Current use of beta blockers (minimum of 7 days washout required)
4. Current use of sedative or hypnotic drugs, including Choral hydrate, Triclofos, and alimemazine tartrate (Vallergan) (minimum of 14 days washout required)
5. Children with a known allergy to melatonin
6. Regular consumption of alcohol (> 3 times per week)
7. Children for whom there are suggestive symptoms of Obstructive Sleep Apnoea Syndrome (OSAS) (such as combinations of snoring, gasping, excessive sweating or

stopping breathing during sleep), physical signs supportive of OSAS (such as very large tonsils/very small chin), or results of investigations suggesting OSAS (such as overnight pulse oximetry or polysomnography) for which the child should be referred to appropriate respiratory or ENT colleagues for specific assessment and treatment
8. Girls or young women who are pregnant at the time of screening (T– 4W)
9. Currently participating in a conflicting clinical study or participation in a clinical study involving a medicinal product within the last 3 months

5.3 Patient Transfer and Withdrawal

In consenting to the trial, patients are consenting to trial treatment, follow-up and data collection. If voluntary withdrawal occurs, the patient (or parent/legal representative) should be asked to allow continuation of scheduled evaluations, complete an end-of-study evaluation, and be given appropriate care under medical supervision until the symptoms of any adverse event resolve or the subject's condition becomes stable.
Follow-up of these patients will be continued through the trial Research Practitioners, the lead investigator at each Centre and, where these are unsuccessful, through the child's GP.

5.3.1 Patient Transfers

For patients moving from the area, every effort should be made for the patient to be followed-up at another participating trial Centre and for this trial centre to take over responsibility for the patient or for follow-up via GP.
A copy of the patient CRFs should be provided for the new Centre and its investigator. The patient (or parent/legal representative) will have to sign a new consent form at the new site, and until this occurs, the patient remains the responsibility of the original centre. The CTU should be notified in writing of patient transfers.

5.3.2 Withdrawal from Trial Intervention

Patients may be withdrawn from treatment for any of the following reasons:
a. Parent/ legal representative (or, where applicable, the patient) withdraws consent for treatment.
b. Unacceptable adverse effects.
c. Intercurrent illness preventing further treatment.
d. Development of serious disease preventing further treatment.
e. Any change in the patient's condition that justifies the discontinuation of treatment in the clinician's opinion.

If a patient wishes to withdraw from trial treatment, centres should document the reason and explain the importance of remaining on trial follow-up and, if willing, to still have data collected as per trial schedule (actigraphy, sleep and seizure dairies, questionnaires etc), or failing this, to attend clinic and allow routine follow-up data to be used for trial purposes. Generally, follow-up will continue unless the patient explicitly also withdraws consent for follow-up (see section 5.3.3). Following withdrawal from trial treatment patients will be treated according to usual local clinical practice.

5.3.3 Withdrawal from Trial Completely

Patients are free to withdraw consent at any time without providing a reason. Patients who wish to withdraw consent for the trial will have anonymised data collected up to the point of that withdrawal of consent included in the analyses. The patient will not contribute further data to the study and the MCRN should be informed in writing by the responsible physician and a withdrawal CRF should be completed. Data up to the time of withdrawal will be included in the analyses unless the patient explicitly states that this is not their wish.

6 ENROLMENT AND RANDOMISATION

6.1 Screening

A log of potential patients will be kept, including individuals who decide not to participate in the study prior to the T-4W clinic visit and inappropriate referrals form community Paediatricians.
Screening will be performed of a patient's possible eligibility for the study and must be documented on the eCRF at the T-4W clinic visit.

Screening at T-4W (See section 8 for T-4W assessments)

1. Fully informed written proxy consent (and assent, where appropriate) to participate in sleep hygiene intervention.
2. Developmental delay indicated and tested by referrer
3. Documentation of attendance at a special school where applicable
4. ABAS questionnaire score with a percentile rank below 7
5. Documentation of previous/current history of melatonin use
6. History of sleep problems (as described in section 5.1)
7. Pregnancy test for sexually active pubertal females who have consented to this procedure.
8. Electronic submission of T-4W eCRF to MCRN CTU within 24 hours of registration.
9. Forward copy of consent/assent forms to MCRN CTU within 7 days of registration.

6.2 Enrolment/ Baseline

Screening at T0W (See section 8 for T0W assessments)

1. A check of compliance with sleep diary and actigraphy; a minimum of 5 out of every 7 days completed
2. Review of severity of sleep problems (as described in section 5.1)
3. A check that they have not been prescribed melatonin since screening
4. Verification that eligibility criteria continue to be fulfilled.

Randomisation Process:

1. Fully informed written proxy consent (and assent, where appropriate)
2. Completion of randomisation eCRF and trial prescription
3. Attend local pharmacy department (see Table 1 for pharmacy contact details)
4. Randomisation and issue of allocated treatment by pharmacy department
5. See section 8 for T0W assessments
6. Electronic submission of T0W eCRF and allocation notification to MCRN CTU within 24 hours of randomisation by the RP
7. Forward copy of consent/assent forms to MCRN CTU within 7 days of randomisation.

Table 1. Pharmacy Contact Details

If any queries about randomisation procedure contact: **Trial Co-ordinator, Charlotte Stockton / Tel 0151 282 4523** **Email: c.stockton@liv.ac.uk**	
Evelina Children's Hospital, London Mr Steve Tomlin, Pharmacy Department, Evelina Children's Hospital, London, SE1 7EH. Tel: 0207 188 9202 Fax: 0207 1889155 Email: stephen.tomlin@gstt.nhs.uk	**Royal Manchester Children's Hospital** Ms Carolyn Davies Royal Manchester Children's Hospital Central Manchester Foundation Trust Clinical Trials Room 4th Floor In-Patient Pharmacy Dept Oxford Road Manchester M13 9WL Tel: 0161 922 2390 Fax: 0161 922 2013 Email: Carolyn.Davies@cmft.nhs.uk
Alder Hey Hospital Ms Catrin Barker Pharmacy Department Alder Hey Children's NHS Foundation Trust (Alder Hey) Eaton Road, Liverpool, L12 2AP Tel: 0151 252 5837 Fax: 0151 220 3885 Email: catrin.barker@alderhey.nhs.uk	**Derbyshire Children's Hospital** Mr Peter Fox Derbyshire Hospitals NHS Foundation Trust Uttoxeter Road, Derby, DE22 3DT Tel: 01332 789 101 Fax: 01332 781 106 Email: peter.fox@derbyhospitals.nhs.uk
University College London Hospitals Mr Simon Keady Pharmacy Department University College Hospital 235 Euston Road London, NW1 2BU Tel: 0845 1555 000 ext.73517 blp.2120 Fax: 0207 691 5749 Email: simon.keady@uclh.nhs.uk	**Nottingham City Hospital** Ms Sarah Pacey Nottingham University Hospitals NHS Trust Nottingham City Hospital Campus Nottingham, NG5 1PB Tel: 0115 9627674 Fax: 0115 9627677 Email: Sarah.Pacey@nuh.nhs.uk
John Radcliffe Hospital Ms Katherine Jacob Pharmacy dept, Level 2 John Radcliffe Hospital Headley way, Oxford, OX3 9DU Tel: 01865 857860 Fax: 01865 857861 Email: Katherine.Jacob@orh.nhs.uk	**Southmead Hospital, Bristol** Ms Annie Chaloner Pharmacy Department Southmead Hospital, Westbury-On-Trym Bristol, BS10 5NB Tel: 0117 959 5492 Fax: 0117 959 5491 Email: ann.chaloner@nbt.nhs.uk
Birmingham Children's Hospital Mrs Claire Norton Pharmacy Management Group Birmingham Childrens' Hospital Steelhouse Lane, Birmingham, B4 6NH Tel 0121 333 9308 Fax 0121 333 9776 Email claire.norton@bch.nhs.uk	
Queen Mary's Hospital, London Mr Andy Fuller Pharmacy Department Southwest London & St. George's Mental Health NHS Trust, Springfield Hospital, Glenburnie Road, London SW17 7DJ Tel: 0208 772 5484 Fax: 0208 682 5822 Email: Andy.Fuller@swlstg-tr.nhs.uk	**Chesterfield Royal Hospital** Mr Martin Shepherd Pharmacy Department Chesterfield Royal Hospital NHS Foundation Trust Calow, Chesterfield, S44 5BL Tel:01246 512 155 Fax: 01246 513 163 Email:martin.shepherd@chesterfieldroyal.nhs.uk

Torbay Hospital Mr Martyn Blundell Pharmacy Department Torbay Hospital Lawes Bridge Torquay, TQ2 7AA Tel: 01803 655 311 Fax: 01803 655 307 Email: martyn.blundell@nhs.net	**Royal Devon and Exeter Hospital** Ms Fiona Hall Pharmacy Clinical Trials Manager Pharmacy Department Royal Devon and Exeter Hospital (Wonford) Barrack Road, Exeter, EX2 5DW Tel: 01392 402 444 Fax: 01392 402 444 / 01392 406 006 Email: Fiona.Hall@rdeft.nhs.uk
Blackpool Victoria Hospital Ms Karen Pollard or Ms Charlotte Armer Pharmacy Department Blackpool Victoria Hospital Whinney Heys Road Blackpool, Lancashire, FY3 8NR Tel: 01253 303109 Fax: 01253 303787 Email: Karen.pollard@bfwhospitals.nhs.uk or charlotte.armer@bfwhospitals.nhs.uk	**Arrowe Park Hospital** Mr Neil Caldwell Pharmacy Department Arrowe Park Hospital Arrowe Park Road Upton, Wirral, CH49 5PE Tel: 0151 678 5111 (ex. 2060) Fax: 0151 604 7066 Email: neil.caldwell@whnt.nhs.uk
Sheffield Children's Hospital Mr John Bane Pharmacy Department Sheffield Children's Hospital Western Bank Sheffield, S10 2TH. Tel: 0114 271 7567 Fax:0114 2768392 E-mail: john.bane@sch.nhs.uk	**Leicester Royal Infirmary** Ms Lisbet Pattrick Paediatric Trials Pharmacy, Windsor building Leicester Royal Infirmary Leicester, LE1 5WW Tel: 0116 2586974 Fax: 0116 2586974 Email: lisbet.pattrick@uhl-tr.nhs.uk
	University Hospital of Wales Ms Annette Stone U.H.W. Pharmacy Heath Park Heath, Cardiff, CF14 4XW Tel: 02920 742 989 Fax: 02920 744 375 Annette.Stone@CardiffandVale.wales.nhs.uk
Southampton General Hospital Ms Joanna Cantle Southampton General Hospital Mailpoint 40, Tremona Rd Southampton, SO16 6YD Tel: 02380 794223, Bleep 1237 Fax: 02380 794855 Email: joanna.cantle@suht.swest.nhs.uk	

7 TRIAL TREATMENT/S

7.1 Introduction

This study is designed as a randomised, controlled, double-blind, multicentre clinical trial comparing the effects of melatonin versus placebo in children with neuro-developmental disorders and impaired sleep. Patients will be treated for a period of 12 weeks and will be followed up throughout this 12 week period.

Patient assessment will be stopped when all patients reach 12 weeks of treatment and/or follow-up.

Patients will be stratified by centre and randomised equally between the two groups:

1. Melatonin
2. Placebo

7.2 Formulation, Packaging, Labelling, Storage and Stability

Melatonin has been sourced by Alliance Pharmaceuticals from a UK fine chemicals manufacturer (SAFC). Manufacture is via a synthetic process to GMP standards.

The proposed formulations will consist of size 2 white opaque capsules at the following strengths:

- 0.5mg
- 2mg
- 6mg
- 12mg

Description and Composition of the Drug Product

Product name: melatonin

Form: oral capsules

Melatonin oral capsules formulation
Melatonin oral capsules, containing melatonin, lactose, and magnesium stearate in a size 2 white opaque, gelatine capsule. The fill weight of each capsule is 200mg. The gelatine is of animal origin.

Capsule contents

Product	**Melatonin**		Lactose DC		Magnesium stearate		Fill weight
	Active		Diluent		Lubricant		
	%	mg	%	mg	%	mg	
0.5mg	0.25	0.5	99.25	198.5	0.5	1.0	200mg
2.0mg	1.0	2.0	98.5	197.0	0.5	1.0	200mg
6.0mg	3.0	6.0	96.5	193.0	0.5	1.0	200mg
12.0mg	6.0	12.0	93.5	187.0	0.5	1.0	200mg
Placebo	n/a		99.5	199.0	0.5	1.0	200mg

Type of container and closure system:
PVC/PVDC blister with aluminium foil top and outer labelled wallet (labels will include study acronym, EudraCT reference number, randomisation number, visit number, site number, instructions for use and storage, lot number and expiry date)

Stability and shelf life
A batch of 0.5mg and 12mg melatonin oral capsules has been put on an ongoing stability programme. Other than storage at temperatures of less than 25^{o}C, no other special storage precautions would be required for this product.

7.3 Ordering of Trial Supplies

Clinical trial supplies can only be delivered to investigator sites once the site has been initiated. This can only be completed once full ethics and regulatory approval has been granted. This must be confirmed by the Trial Co-ordinator acting on behalf of the study sponsor.

Clinical trial supplies should be requested from Penn Pharmaceutical Services Ltd using the MENDS shipment request form (Appendix G). The size of the first shipment to each site will be pre-determined based on the number of patient packs manufactured for the individual site. The first shipment will be approximately half of the total trial supplies for the site. Once trial supplies are running low (e.g. 3 patient packs remaining) an investigator site may place a second order for the remaining quantity of trial supplies. Each site will have a maximum of two deliveries during the study.

The first section of the MENDS shipment request form should be completed – Investigator Site – Request Details. The form should then be faxed to:

Sue Court, Penn Pharmaceutical Services
01495 713743

Supplies will then be delivered to the nominated pharmacist at the investigator site within three to five working days.

7.4 Preparation, Dosage and Administration of Study Treatment/s

7.4.1 Dispensing

For each patient treatment will continue for a maximum period of 12 weeks. Upon randomisation patients will be allocated a treatment pack, which will be retained in the pharmacy department and dispensed as detailed below (see also Fig 2 and Appendix I). Each individual treatment pack will comprise:

- 0.5mg – 12 blister packs, each providing 7 days treatment
- 2mg – 11 blister packs, each providing 7 days treatment
- 6mg – 10 blister packs, each providing 7 days treatment
- 12mg – 9 blister packs, each providing 7 days treatment

When pharmacy dispenses the trial treatments they will add their own local dispensing label, which will include the name and address of the hospital, the patient's name, the date of dispensing and instructions for use.
During the 4-week dose increasing phase, trial treatments will be dispensed in volumes sufficient to provide 14 days treatment (2 blister packs) to allow for unplanned delays in review visits.

Week T0
2 blister packs (14 days supply) of 0.5mg dispensed to family by the RP.

Week T+1
Prior to performing the home visit, 1 blister pack of 0.5mg along with 2 blister packs of 2mg (to provide a total of 14 days supply of each) will be dispensed to the Research Practitioner (RP). During the home visit the RP will evaluate the effectiveness of the treatment dose supplied at T0W in accordance with the dose modification criteria (section 7.9.1) and will either issue an additional blister pack of 0.5mg if this dose is to continue for a further week, or increase the dose and supply 2 blister packs of 2mg for the next week of treatment plus an additional pack.
All unused medication (including omitted doses from the previous week's regimen) will be collected by the RP and returned to pharmacy where they will be retained for destruction by PENN at study completion.

Week T+2
The RP will collect 1 week's supply of trial treatment at the patients current dose level, i.e. the same dose level as was prescribed at the T+1W home visit, in addition to 2 weeks supply of the next scheduled dose increase and 2 weeks supply of the previous dose (if applicable).
During the home visit the RP will evaluate the effectiveness of the treatment dose supplied at T+1W in accordance with the dose modification criteria (section 7.9.1) and will either issue an additional blister pack of the current dose level if this is to continue for a further week, or increase the dose, supplying 2 blister packs of the next dose increment, sufficient for the next week of treatment plus an additional pack. The dose may also be reduced (where applicable) due to the development of unacceptable adverse events or a change in the patient's condition (section 7.9.2). In this case the RP will supply 2 blister packs of the preceding dose.
All unused medication (including omitted doses from the previous week's regimen) will be collected by the RP and returned to pharmacy where they will be retained for destruction by PENN at study completion.

Week T+3
The RP will collect 1 week's supply of trial treatment at the patient's current dose level, i.e. the same dose level as was prescribed at the T+2W home visit, in addition to 2 week's supply of the next scheduled dose increase and 2 weeks supply of the previous dose (if applicable).
During the home visit the RP will evaluate the effectiveness of the treatment dose supplied at T+2W in accordance with the dose modification criteria (section 7.9.1) and will either issue an additional blister pack of the current dose level if this is to continue for a further week, or increase the dose, supplying 2 blister packs of the next dose increment, sufficient for the next week of treatment plus an additional pack. The dose may also be reduced (where applicable) due to the development of unacceptable adverse events or a change in the patient's condition (section 7.9.2). In this case the RP will supply 2 blister packs of the preceding dose.
All unused medication (including omitted doses from the previous week's regimen) will be collected by the RP and returned to pharmacy where they will be retained for destruction by PENN at study completion.

Week T+4
If the maximum daily dose (12mg) has been achieved at the T+3 home visit, the RP will collect sufficient 12mg capsules for the remaining 8 weeks of the trial treatment schedule from the pharmacy department. The RP will also collect 8 blister packs of 6mg capsules in case of a dose reduction.
If the dose level achieved by T+3W is 0.5mg then the RP will collect sufficient capsules to continue on the current dose i.e. the same dose level as was prescribed at the T+3W home visit, in addition to 8 weeks' supply of the next scheduled dose increase.

If the dose level is 2mg or 6mg at T+3W then the RP will collect sufficient capsules to continue on the current dose i.e. the same dose level as was prescribed at the T+3W home visit, in addition to 8 weeks' supply of the next scheduled dose increase and 8 week's supply of the lower dose in case of a dose reduction.

During the home visit the RP will evaluate the effectiveness of the treatment dose supplied at T+3W in accordance with the dose modification criteria (section 7.9.1) and will either issue 7 weeks' supply of the current dose level, if this is to continue for the duration of the study, or increase the dose, supplying 8 blister packs of the next dose increment, sufficient for the remaining 8 weeks of treatment. There is also the possibility of a dose reduction due to the development of unacceptable adverse events or a change in the patient's condition (section 7.9.2). In this case the RP will supply 8 blister packs of the preceding dose.
All unused medication (including omitted doses from the previous week's regimen) will be collected by the RP and returned to pharmacy. At pharmacy, unused medication from the previous week's regimen will be retained for destruction by PENN at study completion. Complete treatment packs taken by the RP to allow dose modifications at the study visit will be returned to pharmacy stores to be held on behalf of the patient, in case they need to be reissued to the patient at a subsequent visit.

Weeks T+5 and T+6
If the dose level prescribed at T+4W is 0.5mg, 2mg, or 6mg, and this is judged to be ineffective by the parent/carer in weeks T+5W or T+6W then an unscheduled visit should be arranged. A decision by the RP to increase the treatment dose may be made at this visit if the dose modification criteria (section 7.9.1) are met. If any of the dose modification criteria are not met, or if there is any doubt, the current dose should be maintained.
Sufficient capsules for the remaining trial period should be supplied and all unused medication at the lower dose level (including omitted doses from the previous week's regimen) should be collected by the RP and returned to pharmacy. At pharmacy, unused medication from the previous week's regimen will be retained for destruction by PENN at study completion. Complete treatment packs will be returned to pharmacy stores to be held on behalf of the patient, in case they need to be reissued to the patient at a subsequent visit.
Dose reductions are permitted at T+5 to T+6 if required (section 7.9.2). If a dose reduction is required an unscheduled visit will be arranged to provide sufficient capsules of the preceding dose for the remainder of the trial period. At pharmacy, unused medication from the previous week's regimen will be retained for destruction by PENN at study completion. Complete treatment packs will be returned to pharmacy stores to be held on behalf of the patient, in case they need to be reissued to the patient at a subsequent visit.

Weeks T+7 to T+11
No dose increases are permitted for the remainder of the trial period. Dose reductions are permitted from T+7 to T+11 if required (section 7.9.2). If a dose reduction is required an unscheduled visit will be arranged to provide sufficient capsules of the preceding dose for the remainder of the trial period. At pharmacy, unused medication from the previous regimen will be retained for destruction by PENN at study completion.

7.4.2 Administration

(i) Oral

One capsule at the prescribed dose is to be administered 45 minutes before the child's age-appropriate 'lights off' or 'snuggle-down-to-sleep' time.

This study is cogniscent of the current significant usage of melatonin on a named patient basis for children with neurodevelopmental disorders. It therefore recognises current clinical practice in those children who are unable or unwilling to swallow capsules. Current clinical practice involves opening the capsules and mixing them in a vehicle such as jam or yoghurt,

and for those patients with feeding tubes, suspending the contents of the capsules in water and administering the solution down the tube.

For participants unable or unwilling to swallow the capsules, the capsules may be opened and the content of the capsule mixed with the following vehicles:

a. strawberry jam, 5ml
b. strawberry yoghurt, 5ml
c. orange juice, 10ml
d. semi-skimmed milk, 10ml
e. water, 10ml

When mixed in such a vehicle, it is recommended that it is administered to the participant immediately. If this is not possible, then it should be kept in the fridge and administered within 30 minutes of mixing. If not administered within 30 minutes the mixture should be thrown away.

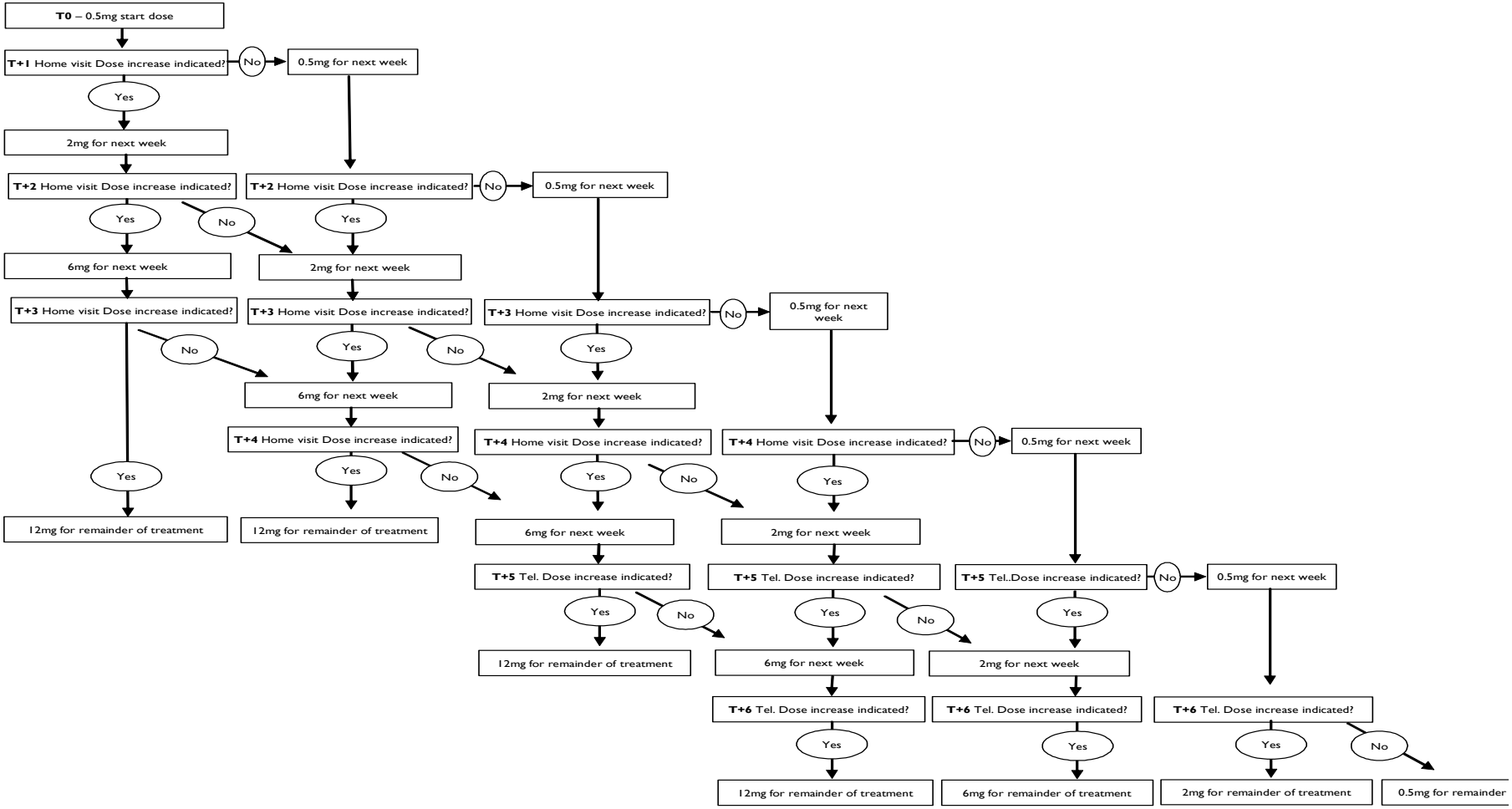
The actual dose delivered will vary due to the method and accuracy of the opening and removal of the powder and the consumption of the food. It is clear from experimental work carried out that the accuracy of the dose is also determined by the dose and that lower dose capsules appear to retain relatively more melatonin drug substance in the shell than higher dose capsules. This method of dosing whilst not ideal is determined by the specific patient group being treated and should not prevent beneficial data being provided to the trial.

It will be noted on the eCRFs for those participants that require study medication to be administered in this manner the vehicle used to administer the study medication. Participants will be encouraged to mix the contents of the capsule with the same vehicle throughout the treatment period.

(ii) Via nasogastric/gastrostomy/jejunostomy tube

For children with nasogastric, gastrostomy or jejunostomy tubes the content of the capsule can be mixed with water, orange juice or semi skimmed milk and administered as normal.

Fig 2. Flow Diagram of Scheduled Treatment Dose Increase Steps



7.5 Unblinding

7.5.1 Unblinding of Individual Participants During Trial Conduct

Unblinding should be considered only when knowledge of the treatment assignment is deemed essential for the child's care by their physician or a regulatory body. In general, unblinding of participants during the conduct of the clinical trial is not allowed unless there are compelling medical or safety reasons to do so.

N.B. If simply ceasing study treatment is a viable option for the patient's care, it should not be necessary for unblinding to occur.

7.5.1.1 Procedure

a. The decision to unblind a single case should be made when knowledge of an individual's allocated treatment is essential to:
   i. enable treatment of serious adverse event/s, or
   ii. enable administration of another therapy that is contraindicated by the trial treatment.
b. Where possible, requests for individual unblinding should be made with the agreement of lead investigators Dr Richard Appleton and/or Dr Paul Gringras (contact should be made via the trial co-ordinator at the MCRN CTU, 0151 282 4523)
c. In the event that it is considered necessary to unblind the participants allocation then the local investigator (or delegated other) should contact the pharmacy department of Alder Hey Hospital, Liverpool where the unblinding codes are held (see below for contact details)

Monday to Friday 0845 to 1730 hours **Saturday/Sunday 0930 to 1600 hours**	**Telephone Pharmacy dispensary:** **0151 252 5311** **Ask for Senior Pharmacist, quoting MENDS unblinding service**
All other times	**Telephone Switchboard:** **0151 228 4811** **Ask that they contact the on-call pharmacist, quoting MENDS unblinding service**

d. Once contacted the Alder Hey Hospital Pharmacy will complete an unblinding CRF and release allocation of the individual patient only. The unblinding CRF will document:
   i. Date information needed
   ii. Detailed reason for unblinding
   iii. Identity of recipient of the unblinding information

   A copy of the unblinding CRF will be forwarded to the MCRN CTU within 24 hours of completion.
e. The local investigator will ensure all necessary CRFs up to the time of unblinding are completed and submitted to MCRN CTU (if possible, completed *before* unblinding is performed). If the reason for unblinding is a serious adverse event all CRFs need to

be submitted to the MCRN CTU within 24 hours; otherwise CRFs can be submitted to MCRN CTU within 7 days.

f. All instances of unblinding should be recorded and reported in writing to the MCRN CTU by the local investigator, including the identity of all recipients of the unblinding information.
g. Allocation should not routinely be revealed to MCRN CTU personnel.

7.5.2 Accidental Unblinding

All instances of inadvertent unblinding should be recorded and reported in writing to the MCRN CTU by the local investigator. Reports to include:

1. Date of unblinding
2. Detailed explanation of circumstances
3. Recipients of the unblinding information
4. Action to prevent further occurrence
5. Allocation should not be routinely revealed to MCRN CTU personnel.

7.5.3 At Trial Closure

The end of the trial will be considered as the date of the final database lock, however the trial may be closed prematurely by the Trial Steering Committee, on the recommendation of the Data Monitoring Committee, for reasons such as clear differences between safety of trial treatments. Upon trial closure the Alder Hey Hospital pharmacy department will return unblinding codes to the MCRN CTU. MCRN CTU will notify local investigators in writing of unblinding information for patients under their care. A copy of this notification should be placed in the medical records and a copy retained in the site file. It is the responsibility of the local investigator to notify trial participants of their allocated treatment.

7.6 Accountability Procedures for Study Treatment/s

Throughout the study, patients will always be provided with a 7 day excess of their current treatment dose to allow for any unexpected delay in home or clinic visits. At randomisation (T0) the RP will collect 2 blister packs (7x0.5mg capsules in each) from pharmacy from the next patient pack to be assigned. The dispensing pharmacist will put the blister packs into a blank carton and put their local dispensing sticker (including patient name, patient address, pharmacy address and date) on to the carton, and will complete, sign and date the accountability log. The RP will also sign and date the accountability log. The RP will record the randomisation number on the pack in the eCRF. At each subsequent visit the RP will be provided with 1 blister pack (7 capsules) of the current dose, 2 blister packs of the next higher dose (if applicable) and 2 blister packs of the lower dose (if applicable, in case of dose reduction). The RP will ask the parents/guardians whether any doses have been missed during the preceding week and will check that this information corresponds with the number of capsules remaining in the blister pack. At each visit any extra medication and any used packages will be returned to the site pharmacy by the RP and will be signed for by the pharmacist who will record the number of capsules returned (See drug accountability log in Appendix I). At the end of the trial all medication will be returned to PENN for central destruction.

7.7 Assessment of Compliance with Study Treatment/s

Weeks T0 to T+4 (RP home visits)

The RP will collect all unused medication from the previous week at each home visit and a pill count will be conducted and recorded to determine that sufficient doses have been administered to enable dose increase, in accordance with section 7.9.1

All unused medication collected by the RP will be returned to pharmacy where they will be retained for the duration of the trial; at the end of the trial they will be returned to PENN for destruction.

Week T+11 (RP Home visit)

The RP will collect all unused medication from weeks T+5W to T+11W and a pill count will be conducted and recorded.

All unused medication collected by the RP will be returned to pharmacy where they will be retained for the duration of the trial; at the end of the trial they will be returned to PENN for destruction.

Week T+12 (clinic review)

The blister pack for week T+12W treatment regimen will be collected during the final trial assessment clinic visit and a pill count will be conducted and recorded. Any unused medication will be returned to pharmacy and retained for the duration of the trial; at the end of the trial returned to PENN for destruction.

Early withdrawal

If a patient wishes to withdraw from trial treatment, all unused medication will be collected and a pill count conducted and recorded. The unused medication will be returned to pharmacy and retained for the duration of the trial; at the end of the trial they will be returned to PENN for destruction.

7.8 Concomitant Medications/Treatments

7.8.1 Medications Permitted

Details of concomitant medication will be collected on the CRF at T0W and reviewed during weekly assessments (either during home visit/telephone call/clinic visit) between T0W and T+12W. The following concomitant medications, recorded at T0W, are permitted and must be documented on the eCRF:

- all anti-epileptics
- all stimulants
- all anti-depressants
- all mood changing drugs other than beta blockers
- all antibiotics

7.8.2 Medications Not Permitted/ Precautions Required

The following are not permitted for the duration of the trial period. If unavoidable for clinical reasons then the patient will be withdrawn from the trial:

- melatonin (other than the study treatment)
- all beta-blockers
- consumption of alcohol
- sedative / hypnotic drugs (including chloral hydrate, alimemazine tartrate (Vallergan) and Triclofos)

The following drugs in particular should not be commenced (although if patients have been treated with them at a stable dose for 2 months prior to the date of screening they can be entered into the study), if possible, during the trial period. However if necessary their use is permitted and should be documented on the eCRF:

- any benzodiazepines
- amisulpride (Solian)
- chlorpromazine (Largactil)

- haloperidol (Haldol)
- olanzapine (Zyprexa)
- risperidone (Risperdal)
- sertindole (Serdolect)
- sulpiride (Sulpidil, Sulpor)
- thioridazine (Melleril)
- trifluoperazine (Stelazine)

7.8.3 Data on Concomitant Medication

Dose and names of all concomitant medication should be documented on the eCRF at T0W. This will be reassessed weekly by the RP throughout trial participation; during home visits, telephone contact or clinic review. Any new medications introduced or changes to medications during the trial period should be documented on the eCRF.

7.9 Dose Modifications

7.9.1 Stepped dose increases (Weeks T+1 to T+4 (also T+5 and T+6)

At each home visit the RP will review the sleep and seizure diary and Treatment Emergent Signs and Symptoms (TESS; section 8.4.2) in order to make an overall assessment of treatment effect. If a dose increase is to be undertaken the following criteria should all be met:

(i) absence of Serious Adverse Events
(ii) a minimum of 5 of 7 days completed in the sleep diary
(iii) no 'significant increase'* in seizure activity (where applicable)
(iv) child having received at least 5 of the possible 7 doses in the current week and
(v) a) child not falling asleep within one hour of 'lights off' or 'snuggling down to sleep' at age-appropriate times for the child in three nights out of five **, and/or
b) child having less than 6 hours of continuous sleep in three nights out of five.

* Defined as a doubling in seizure activity over the preceding four weeks
** This will be the child's usual bedtime based upon the family's normal routine

If any of the criteria are not met, or if there is any doubt, the current dose should be maintained.

7.9.2 Dose reductions, interruptions or permanent discontinuation

The decision to reduce, interrupt, or discontinue trial therapy is at the discretion of the treating clinician. Doses may be reduced, interrupted or discontinued at any time during the trial period for reasons such as unacceptable adverse effects (e.g. unacceptable increase in daytime fatigue, unacceptable behavioural change, doubling in the number of seizures during the preceding four weeks, unacceptable increase in number or severity of headaches), intercurrent illness, development of serious disease or any change in the patient's condition that justifies the modification of treatment in the clinician's opinion.
Prior to modifications of trial therapy the RP will consult (via telephone) with the local PI (or appropriate clinician listed on the site delegation log) or one of the lead investigators (Dr Richard Appleton or Dr Paul Gringras). If a dose reduction is agreed upon and the decision is made during the home visit then the family will be provided with the preceding dose.
In the event that neither a local investigator nor one of the lead investigators are available until the next working day, that evenings dose of melatonin will be omitted, until the decision to modify the dose has been confirmed by an appropriate clinician. At this point if a decision to reduce the dose is confirmed then an additional unscheduled home visit will be arranged as soon as possible in order for the RP to provide sufficient melatonin of the previous strength for the time period until the next scheduled home or clinic visit. Any doses of

melatonin scheduled between the time of the decision to lower the dose and the day of the unscheduled visit would be omitted. An unscheduled visit would also be arranged if a dose reduction is thought to be required following a scheduled telephone call. Modifications of trial therapy should be documented on the eCRF.

7.10 Co-enrolment Guidelines

To avoid potential confounding issues, ideally patients should not be recruited into other trials. Individuals that have participated in a trial testing a medicinal product within the three months preceding screening will be ineligible for the study. Where recruitment into another trial is considered to be appropriate and without having any detrimental effect on the MENDS trial this must first be discussed with the coordinating centre (MCRN CTU) who will contact the lead investigators (Dr Richard Appleton/Dr Paul Gringras).

8 ASSESSMENTS AND PROCEDURES

8.1 Summary

All patients will be recruited from outpatient clinics of specialist centres. Potential participants will generally be identified by community paediatricians, who will refer to specialist centres for review of sleep disorders. The community paediatricians will be engaged to provide potential participants with written information about the trial, including contact details if they require further information, and arrange for an out patient clinic appointment in the usual way.

Following fully informed written consent and assent (if appropriate) (Section 11.3) all eligible patients will be registered for the study and the family will be provided with a standardised booklet on basic sleep hygiene and behavioural techniques shown to help reduce sleeping difficulties, but no other intervention (behavioural, pharmacological or homeopathic), to try and improve their child's sleep. They will also be shown how to complete a 24-hour sleep diary and will be asked to complete this continuously over the next four weeks. In addition to this an actigraph will be provided, which the child will wear for the next four weeks to provide baseline data relating to wake and sleep periods.

Two weeks after registration a home visit will be undertaken by the RP, who will review progress with the sleep hygiene intervention. No formal assessment of progress will be undertaken and no further intervention will be commenced. A sub-study is also being undertaken that involves genotyping of all children initially recruited to the project with sleep disorders and developmental delay. As preliminary data suggests that autism may be particularly strongly associated with some of the genetic variants under investigation, we need to define this subgroup with more precision, this will be done using the Social Communication Questionnaire (SCQ) although it is acknowledged that this is a screening and not a diagnostic tool. Collection of DNA (see Appendix K) and completion of the SCQ will be subject to a separate consent and assent (if appropriate) process that will be undertaken at this home visit. Equipment will be provided for salivary sampling, which will be undertaken on the evening prior to the randomisation visit.

The child will be seen again in clinic a minimum of 4 weeks after registration and, if still fulfilling eligibility criteria, will be randomised into the study. The sleep hygiene period can be extended to a maximum of 6 weeks if required to allow flexibility in the scheduling of the randomisation clinic visit. Randomisation will require additional fully informed written consent and assent (if appropriate) (Section 11.3).

The trial duration for each participant is 12 weeks from date of randomisation and it is intended that all randomised patients will receive trial medication throughout their participation. At randomisation each patient will be allocated their own 'individual patient package' containing either melatonin or placebo. These packages will be retained in the pharmacy department of the relevant institution and issued on a weekly basis dependent upon dose to be administered. The child will be given the first dose and kept on that dose for a minimum of seven days. For the next three weeks and at each one-week interval during this time, the child's sleep disorder will be reviewed by the RP during home visits and the medication either left unchanged, increased to the next dose increment based upon the protocol dose modification criteria (see section 7.9.1) or decreased due to the presence of adverse events (see section 7.9.2). The decision to increase medication will be based upon the protocol dose modification criteria: (i) absence of Serious Adverse Events; (ii) a minimum of 5 of 7 days completed in the sleep diary; (iii) no significant increase in seizure activity (where applicable); (iv) child having received at least 5 of the possible 7 doses in the current week; (v) a) child not falling asleep within one hour of 'lights off' or 'snuggling down to sleep' at age-appropriate times for the child in three nights out of five, and/or b) child having less than 6 hours of continuous sleep in three nights out of five.

There are a maximum of 3 dose increments after the starting dose of 0.5 mg, through 2.0mg, 6.0mg and up to a maximum of 12.0mg. After seven days, the child will either be maintained on that dose if the sleep disorder has improved (i.e. the fifth dose modification criteria is no

longer met) or increased to the next dose if all dose modification criteria are met (see section 7.9.1). This process will be repeated after a further seven days until the third home visit after commencing study drug. If doses are increased at each home visit, the maximum dose threshold will be achieved by T+3W and for the remainder of the study, the child will remain on the dose achieved by the fourth week of treatment unless a reduction is indicated when reviewed at subsequent follow-up (see section 7.9.2). For children who have not achieved the maximum dose level in week T+3W, a dose increment at T+4W may also be considered. Dose increases in weeks T+5/T+6W are permitted with appropriate clinical review (see section 7.4.1) but are not permitted beyond this time.

8.2 Schedule for Follow-up

(See also Table 2)

TIME (weeks)	**Study Schedule**
T–4W:	**Clinic visit (Clinician and RP).** In the outpatient department, potential participants will be screened by the clinician and RP and those identified as being eligible for entry into the study on the basis of meeting the inclusion and exclusion criteria will be invited to allow the trial RP to complete assessments and provide the sleep hygiene/behavioural information. Following fully informed written consent (by RP or investigator) they will be registered in the study and allocated a unique registration number. At this stage participants are consenting only to be registered and undergo the 4 week sleep hygiene intervention and assessments. Adhering to a scripted dialogue (Appendix H), the RP will provide the family with a standardised booklet on basic sleep hygiene and behavioural intervention. No other intervention (behavioural, pharmacological or homeopathic) to try and improve their child's sleep will be initiated. They will be shown how to complete a 24-hour sleep diary and will be asked to maintain a continuous sleep diary record over the next 4 weeks. Additionally, for patients with a diagnosis of epilepsy a seizure diary will also be maintained. The RP will supply the actigraph to be applied for the next four weeks, explaining how it is worn and operated. **The following questionnaires and assessments will be carried out:** • Adaptive Behaviour Assessment System (ABAS) • Children's Sleep Habits Questionnaire (CSHQ) • Composite Sleep Disturbance Index (CSDI) Arrangements will be made for the RP to visit them at home at T -2W (i.e. after 2 weeks of basic sleep hygiene and behavioural intervention)
T–2W:	**Home visit 1 (study nurse).** The RP will visit the home to discuss progress, although no additional sleep intervention advice will be provided. The actigraph will be downloaded, visually compared with the sleep diary and re-initialised. Reasons for major discrepancies with the sleep diary will be recorded. **For those who consent (separate consent process carried out at this visit), the following will be carried out:** • Collection of DNA sample (saliva sample) • Completion of Social Communication Questionnaire Equipment will be provided along with verbal and written explanations for undertaking the salivary melatonin collection, which will be carried out on the evening prior to the T0W clinic visit and at T+10W (see

section 8.6.3 and Appendices D and E [instructions for collection]). The analysis of both sets of samples will be carried out at the same time at the end of the study.

T0W: **Clinic visit (Clinician review).** Children will be reviewed in the outpatient clinic and their sleep pattern (as reported by their family) and sleep diaries will be reviewed to decide whether they are still eligible for the study. Actigraph data will be downloaded and visually compared with the sleep diary but will not be analysed at this time and the actigraph will be removed. Reasons for major discrepancies with the sleep diary will be recorded. Prior to T0 consent and randomisation a single sheet form will be completed to evaluate which aspects of the advice given in the sleep hygiene booklet parents have put into practice. The responses to this evaluation will not influence whether or not the child is randomised.
Assuming the child continues to fulfil the entry criteria and fully informed written consent is provided; the child will then be randomised into the study.
The following baseline questionnaires and assessments will be carried out after consent and prior to randomisation:

- Composite Sleep Disturbance Index (CSDI)
- Children's Sleep Habits Questionnaire (CSHQ)
- Family Impact Module of PedsQL™
- Epworth Sleepiness Scale
- Aberrant Behaviour Checklist (ABC)

Upon randomisation the child will be allocated a unique randomisation number and their trial treatment. The randomisation number supersedes the registration number and will be used on all subsequent trial records.

Two week's supply of study medication will be dispensed (to allow for any delay in visit 2); to be administered 45 minutes before the child's age-appropriate 'lights off' or 'snuggle-down-to-sleep' time.

T+1W: **Home visit 2 (RP).** Child and sleep diary reviewed; medication increased or maintained*, based upon sleep diaries; TESS review; seizure diary review.
* Decision based upon the protocol dose modification criteria (Section 7.9)

T+2W: **Home visit 3 (RP).** Child and sleep diary reviewed; medication increased, maintained or decreased according to dose modification criteria (Section 7.9), based upon sleep diary; TESS review; seizure diary review.

T+3W: **Home visit 4 (RP).** Child and sleep diary reviewed; medication increased, maintained or decreased according to dose modification criteria (Section 7.9), based upon sleep diary; TESS review; seizure diary review.

T+4W: **Home visit 5 (RP).** Child and sleep diary reviewed; medication dose increased, maintained or decreased according to dose modification criteria (Section 7.9), based upon sleep diary; TESS review; seizure diary review.

T+5W to T+6W **Weekly telephone call (RP).** Child and sleep diary reviewed. Seizure diary (if applicable) and TESS review. Medication dose increased, maintained or decreased according to dose modification criteria (Section 7.9).

T+7W to T+9W **Weekly telephone call (RP).** Child and sleep diary reviewed. Seizure diary (if applicable) and TESS review. Medication dose maintained, no further increases permitted. Dose reductions are permitted if required (Section 7.9.2).

T+10W **Weekly telephone call (RP).** Child and sleep diary reviewed. Seizure diary (if applicable) and TESS review. Reminder to obtain salivary melatonin assay during this week. **Second and final collection of saliva takes place at the beginning of the eleventh week (ideally on the evening following the T+10 telephone call) of treatment and MUST occur one night after NO melatonin that or the previous night.**

T+11W: **Home visit 6 (RP).** Child and sleep diary reviewed. Seizure diary (if applicable) and TESS review. Application of actigraph for final week of study treatment. RP will collect unused medication from weeks T+5W to T+11W (sufficient capsules to be retained by family for final week of therapy).

T+12W: **Clinic visit (Clinician review).** Study completion. Child and sleep diary reviewed. Seizure diary (if applicable) and TESS review. Actigraph data downloaded and visually compared with the sleep diary. Reasons for major discrepancies with the sleep diary recorded. Actigraph unit collected; parents to complete the same questionnaires as completed at T0W

The RP will be available by telephone between the formal reviews to give advice and support regarding the practicalities of the study but will not give advice on sleep management.

Table 2. Schedule of Study Procedures

Time (T) (Weeks)		-4	-2	0*	1	2	3	4	5 & 6	7 to 9	10	11	12	
Procedures		**Screening (Clinic visit)**	**Home visit**	**Clinic visit**	**Home visit**	**Home visit**	**Home visit**	**Home visit**	**Tel. call**	**Tel. call**	**Tel. call**	**Home visit**	**Study completion (Clinic visit)**	**Premature Discontinuation**
Signed Informed Consent **		X[1]	X[2]	X[3]										
Adaptive Behaviour Assessment System		X												
Assessment of Eligibility Criteria		X	X	X										
Review of Medical History		X		X										
Registration for 4-week Sleep Hygiene		X												
Review of Concomitant Medications				X	X	X	X	X	X	X	X	X	X	X
Discussion and issue of sleep hygiene booklet		X												
Social Communication Questionnaire			X											
Sleep hygiene booklet evaluation form				X										
Randomisation				X										
Children's Sleep Habits Questionnaire		X		X										
Composite Sleep Disturbance Index (CSDI)		X		X									X	
Family Impact Module of PedsQL™				X									X	
Epworth Sleepiness Scale				X									X	
Aberrant Behaviour Checklist (ABC)				X									X	
Sleep and seizure diary (if applicable)		X	X	X	X	X	X	X	X	X	X	X		
Actigraph is worn (actigraphy)		X	X	X								X		
Study Intervention				X	X	X	X	X	X	X	X	X		
Stepwise increase in treatment dose					(X)	(X)	(X)	(X)	(X)					
Physical Exam	Complete	X		X									X	(X)
	Symptom-Directed				(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)		
	Vital Signs, weight, height	X		X	(X)	(X)	(X)	(X)	(X)	(X)	(X)	(X)	X	(X)
	Occipital head circumference	X												
Assessment of Adverse Events					X	X	X	X	X	X	X	X	X	X
Special Assay or Procedure	Salivary Melatonin			X							X			
	DNA (salivary sample)		X											

*At baseline, all procedures should be done before study intervention. **Consent to: [1]Sleep hygiene; [2]DNA collection; [3]Randomiastion (X) – As indicated/appropriate.

8.3 Procedures for Assessing Efficacy

Duration of night-time sleep and sleep latency will be recorded by subjective (sleep diary) and objective means (actigraphy).

8.3.1 Sleep Diary

Each A4 page of the sleep diary covers a period of one week, with one column per day. Parents document their child's bed time, time they fall asleep and final time that they wake up in the morning on the form. Parents also record the time and duration of actigraph removal, daytime naps and awakenings during the night. The diary therefore allows parental perception* of their child's sleep periods to be documented and can be crosschecked with the actigraph data.

Sleep diaries will be completed continuously between T-4W and review at T0W, continuing until study completion (T+12W) for those patients who proceed with randomisation at T0W. They will be collected by the RP during home visits or clinic attendance. The RP will retain a photo-copy of these records but will forward originals to the MCRN CTU.

*Sleep diary records parental perception of a child's sleep. Parents are not required to differentiate between periods where the child is actually asleep and periods where the child is awake but quiet e.g. not disturbing the rest of the household. Therefore parents do not have to stay awake to complete the sleep diary.

8.3.2 Actigraphy

Actigraphy is the use of accelerometers to measure human movement. This has been used world wide in a variety of research and clinical situations. The actigraph is worn on the wrist and the movement of the wrist is monitored continuously whilst it is being worn. The actigraph is very light weight and can be used on individuals of all ages for long periods of time. Wrist movement data is processed within the unit and by subsequent software programs to give an indication of general activity levels of a participant.

The use of actigraphy in sleep monitoring is now well established[29;36]. This is based on the use of algorithms to predict if the participant is asleep or awake based on levels or lack of movement. During consolidated sleep periods this can give information on for instance; total sleep and wake times, sleep onset latency, sleep efficiency and sleep quality. As the actigraph measures movement, further indicators are also available that are not available in overnight polysomnography studies nor from sleep diaries, these include: the amount of movement in sleep, the fragmentation index, circadian rhythm data, daytime nap analysis and activity during the daytime.

The actigraph should be worn continuously day and night for the first 4 weeks and the final week of the 16 week study period. The actigraph may be worn during bathing or showering. It can be worn on either wrist but the same wrist should be used throughout the study.

The RP will supply actigraphs with preloaded identification information in them for use with the individual child. The actigraph should be given to the participant at T-4W (the start of the sleep hygiene intervention) and will be retained until T0. Actigraphs will be downloaded and / or re-initialised at the T-2W andT0W visits. The

RP will download the actigraph data to a PC, via an Actigraph Reader, during home / clinic visits. On return to the office, or at the time, the RP will visually compare the output with the sleep diaries and will discuss any discrepancies with the parents on the telephone or at the visit. Reasons for major discrepancies with the sleep diary will be recorded. At T0W the actigraph will be removed, retaining it at site until T+11W when the actigraph is worn for the final week of trial treatment. Actigraphy data will be analysed when all patients have completed follow-up. Using the actigraph Sleep Analysis software the following information will be recorded for each night of the study period:

- total sleep time
- total wake time
- sleep onset latency
- number of awakenings

The actigraph monitor measures and stores data regarding body movements. Movements are scored in 1 minute epochs; all epochs that are scored above a pre-set threshold (sensitivity level) are scored as 'wake' and those that are below this threshold are scored as 'sleep'. The threshold is not set on an individual basis.
The start of sleep is determined from the actigraph as the first 10 minute interval, after bedtime (recorded in the diary) were there is no more than 1 epoch that is above the threshold (automatically calculated by the software) for determining wake, the software then considers the first minute of this 10 minute period as the time of sleep onset.
Any sleep interruptions will be determined by the actigraph by searching for 10 minute intervals in which activity in more than 1 epoch is above the threshold set automatically for determining 'wake'
Final wake-up time is recorded by parents in the sleep diary to the nearest minute
Sleep off-set is determined to be the last 10 minute period prior to 'final wake-up time' in which there was no more than 1 epoch that was above the threshold for determining wake.
The last minute of this 10 minute period will provide the sleep off-set time.
Total night-time sleep is calculated as the sum of all epochs scored as sleep from sleep onset to sleep offset.
As the actigraphy watch defines periods of sleep as periods with little/no activity it is acknowledged that periods of restless sleep may be interpreted by the unit as periods of wake. This may be of particular issue for children with motor problems. Interpretation of the actigraphy data will be informed by the sleep diaries.

8.4 Procedures for Assessing Safety

8.4.1 Expected Adverse Events (Treatment Emergent Signs and Symptoms [TESS])

Assessment of adverse effects will be undertaken weekly between weeks T0W to T12W. These reviews will be performed by the investigator at clinic attendance or the RP during home visits or via telephone assessment. Adverse effects will be assessed using Treatment Emergent Signs and Symptoms (TESS). The TESS evaluation will include the following specific signs and symptoms:

- somnolence (drowsiness)
- increased excitability
- mood swings
- seizures (new presentation or exacerbation)*

- rash
- hypothermia
- cough
- other adverse effects not listed will also be documented; the Investigator's Brochure should be referred to when assessing causality and expectedness.

*A seizure diary will be given to the parents of those children who have an established diagnosis of epilepsy, whether or not they are receiving any antiepileptic medication (see Section 8.4.2).

Signs and symptoms will be graded and reported as; no symptoms (score 0); mild symptoms (score 1); moderate symptoms (score 2) and severe symptoms (score 3). Seriousness and causality will also be assessed by the reporting researcher (see section 10).

8.4.2 Seizure diaries

Seizure diaries will be completed between T-4W to T0W and reviewed at randomisation (T0W). Post randomisation they will be reviewed, at weekly intervals for the first four weeks during home visits by the RP (T1W, T2W, T3W, T4W), at the final home visit (T11W) and at the clinic visit at week 12 (T12W). Seizure status will also be discussed during telephone review by the RP in weeks T5W to T10W. Information will be collected on the number of seizures, the type and whether the child was asleep or awake at the time of the seizure.

8.5 Substudies

8.5.1 Genetic Study

Whilst we know that melatonin secretion is highly heritable in humans (suggesting genetic reasons may be more important than environmental factors) no specific genetic cause had been identified. Mutations in ASMT, which encodes the last enzyme in the pathway that produces melatonin have now been described[37]. Corresponding low levels of melatonin and sleep disorders are seen in the families where these mutations are found. The link is particularly strong in populations with learning difficulty and autism, where it has been speculated that additional mutations in neuroligins lead to an increased susceptibility to sleep disorders.

The ability to detect genetic variations that account for abnormal melatonin production has been described by the Human Genetics and Cognitive Functions laboratory at the Pasteur Institute, France, and some candidate genes have been identified. The first group of candidate genes are those encoding the enzyme synthesising melatonin (TPH2, AA-NAT, ASMT) and the receptors of the melatonin (MTNR1A, MTNR1B, GPR50). The second group are genes thought to play a role in the aetiology of both autistic spectrum disorders and learning difficulties, both of which markedly increase the risk of sleep disorders (NLGN, MAOA, MAOB, COMT, SLC6A4, GABAR).

We are working with the Pasteur Institute on a genome-wide association (GWA) study, the aim being to identify genetic variants, initially within the aforementioned candidate genes and then also across the remaining genomic regions, associated with abnormal melatonin production and subsequently with sleep disorder.

Single Nucleotide Polymorphisms (SNPs) across the genome will be genotyped using the patient's DNA from a simple saliva sample. Genotyping will be undertaken using Illumina's HumanCNV370-Duochip ('370k chip') by the Human Genetics and

Cognitive Functions team, who already have an impressive track record in this field and all the facilities for rapid, blinded, genotyping. The 370k chip captures 81% and 68% of HapMap genetic variants at $r^2 > 0.8$, in Caucasian and Asian populations respectively. It therefore provides high genomic coverage of the known human genome SNPs.

In order to make sense of genotype phenotype correlations, large populations, defined by as much objective data as possible, are required. The MENDS study is gathering objective actigraphic and salivary melatonin data on children who enter the study and the population we are studying is precisely the group where genetic mutations specific to melatonin production might be expected. The MENDS sub-study aims to address the following:
(i) what is the nature of any association between sleep problems and melatonin levels?
(ii) can we identify genetic markers associated with the severity of the sleep problem and/or melatonin level?
(iii) can we identify genetic markers that are associated with an individual's ability to synthesise melatonin?
(iv) can we identify genetic markers that are associated with an individual's response to melatonin treatment in sleep disorders?

This sub-study will therefore involve genotyping of all children initially recruited to the project with sleep disorders and developmental delay. As preliminary data suggests that autism may be particularly strongly associated with these genetic mutations, we will precisely define this subgroup using the Social Communication Questionnaire. If the questionnaire suggests the presence of autism in a child with no previous diagnosis a letter will be sent to the referring clinician highlighting this (Appendix J).

8.5.2 RECRUIT Study

It is proposed that MENDS will involve a qualitative substudy "Processes in recruitment to randomised controlled trials (RCTs) of medicines for children (RECRUIT)". RECRUIT was approved in its own right by the North West MREC at its meeting on 2 March 2007 (REF 07/MRE08/6).

RECRUIT will be examining communication processes in the recruitment of participants to MENDS with the aim of identifying strategies for subsequent trials of medicines for children to improve trial recruitment and conduct. RECRUIT will involve:

a) Routine audio-recording of MENDS discussions (consultations) between families and practitioners (trial recruiters).
b) Follow-up interviews with up to 8 families (parents and children where aged 7 or over) who agree to participate in MENDS.
c) Follow-up interviews with up to 8 families (parents and children where aged 7 or over) who decline participation in MENDS.
d) Follow-up interviews with up to 8 trial recruiters involved in approaching families to take part in MENDS.

Collection of data for a) will be facilitated by MENDS staff who will *routinely* seek permission to audio-record recruitment consultations from the families whom they approach for MENDS. Data for b, c and d will be collected by the Research Associates (RAs) employed on RECRUIT, who will be entirely independent of MENDS.

If permission for audio-recording is declined by a family the recruitment consultation will not be recorded. If permission is given the recruiter will activate an audio-recorder. At the end of the MENDS recruitment consultation the recruiter will discuss RECRUIT with the family and seek their permission to pass their details to one of the RAs employed on RECRUIT, who will then make contact with families and obtain written informed consent for participation in the RECRUIT study. Recordings from families who decline RECRUIT will be erased as soon as practicable. All families who express an interest in RECRUIT but are not selected for follow-up interview will be contacted by letter to thank them and inform them that their recordings have been erased. Audio-recordings of the recruitment consultations will only be released to the RECRUIT RAs after the consent of participants has been obtained.

All interviews for RECRUIT will be conducted by experienced RAs with proven skills in the conduct of research in sensitive settings. Any distress during the interviews will be managed with care and compassion by the RAs, and participants will be free to decline to answer any questions that they do not wish to answer or to stop the interviews at any point. The RAs will receive appropriate training and follow a clear protocol for managing participants whose level of distress gives cause for concern. Any such families will be supported in obtaining appropriate help. If necessary, and after discussion with the participant, the lead clinician responsible for the child's care will be informed.

To allow MENDS to become established and avoid the initial “teething” phase that most trials experience, sampling for RECRUIT will not begin until the trial has been recruiting for approximately 4 months. Sampling to RECRUIT (and therefore the routine audio-recording of trial consultations) will roll from trial site to trial site in blocks of up to 3 months’ duration, with planned suspensions if accrual to RECRUIT allows. This will help to minimise the numbers of families who are approached but not selected for RECRUIT. Concentrating sampling at particular sites in time-limited blocks, with the possibility of planned suspensions, will minimise the impact of RECRUIT on MENDS and the risk of overburdening particular sites. It will also facilitate liaison with the sites and assist recruiters in routine audio-recording of consultations.

8.6 Other Assessments

8.6.2 Sleep Habits, Quality of Life and Cognitive Function

8.6.2.1 Children’s Sleep Habits Questionnaire

A comprehensive, parent-report sleep screening instrument designed for school-aged children, the Children's Sleep Habits Questionnaire (CSHQ) yields both a total score and eight subscale scores, reflecting key sleep domains that encompass the major medical and behavioural sleep disorders in this age group. The questionnaire takes 10 minutes to complete and is carried out at T-4W and T0W. The RP will enter data from the CSHQ onto the corresponding eCRF and retain a photo-copy of the questionnaire at site. Original documents will be forwarded to the MCRN CTU.

8.6.2.2 PedsQL™ Family Impact Module

The PedsQL™ Family Impact Module takes approximately 5 minutes to complete and will be undertaken at T0W and T+12W. It is designed to measure the impact of paediatric chronic health conditions on parents and the family. It measures parent self-reported physical, emotional, social, and cognitive functioning, communication, and worry. The Module also measures parent-reported family daily activities and family relationships. The RP will enter data from the PedsQL™ Family Impact Module onto the corresponding eCRF and retain a copy of the questionnaire at site. Original documents will be forwarded to the MCRN CTU.

8.6.2.3 Epworth Sleepiness Scale

The Epworth Sleepiness Scale takes 2-3 minutes to complete and will be undertaken by the caregiver at T0W and T+12W. This is a simple, self-administered questionnaire, which provides a measurement of the caregiver's general level of daytime sleepiness. The RP will enter data from the Epworth Scale into the corresponding eCRF and retain a copy of the questionnaire at site. Original documents will be forwarded to the MCRN CTU.

8.6.2.4 Aberrant Behaviour Checklist (ABC)

The Aberrant Behaviour Checklist is completed at T0W and T+12W; taking 15 to 20 minutes, and is an instrument for assessing individual baseline behaviour and for evaluating behavioural change. The RP will enter data from the completed ABC onto the corresponding eCRF and retain a copy of the questionnaire at site. Original documents will be forwarded to the MCRN CTU.

8.6.2.5 Composite Sleep Disturbance Index (CSDI)

The Composite Sleep Disturbance Index is completed at T-4W, T0W and T+12W and takes 2 to 3 minutes to complete. This measure is based on allocating scores according to the frequency and severity of sleep problems.

Table 3: Scoring criteria for the components of the Composite Sleep Disturbance Score

Score	**0**	**1**	**2**
Frequency	<1 per week	1-2 times per week	3+ times per week
Duration	Few minutes	≤30 minutes	31 minutes +

Applying the scoring criteria of Table 3 the CSDI will be calculated as follows: Settling problems, night waking, early waking (before 5am) and co-sleeping will be measured in terms of weekly frequency and settling and nightwaking problems will also be assessed in terms of the nightly duration of the problem. Using the scores shown in Table 3 scores will range from 0 to 12.

8.6.3 Special Assays or Procedures

8.6.3.1 Salivary melatonin assay

Salivary melatonin levels will be measured on each patient at two time points in the study; at, T-1W (i.e. the evening prior to the randomisation clinic visit, T0) and at T+10W (i.e. melatonin is not given on the evening of the telephone call and the salivary sampling is carried out the following evening). This should allow accurate categorisation of which children are physiologically phase delayed at the beginning of the study, which may prove to be an important variable when comparing responders to non-responders in a secondary analysis.

Methods

Saliva samples will be collected hourly from 5pm until bedtime on two separate occasions at:

- **T-1W,** on the night prior to the randomisation clinic visit
- **T+10W,** on the night AFTER a dose of trial treatment has been omitted and *on which night no trial medication should be given* (i.e. two doses will be missed at the beginning of the eleventh week of study treatment)

Salivary samples should be collected (instructions to participants Appendix D and researchers Appendix E) and stored by the parent in a domestic freezer at a maximum temperature of - 18°C and collected by the RP for storage until trial completion when they will be placed in dry ice and transported to the School of Biomedical and Molecular Sciences, University of Surrey, Guildford for blinded analysis.

Details of analysis

Assay protocols can be found in Appendix F. The time of dim light melatonin onset (DLMO) will be calculated using 2 x SD of the individuals baseline melatonin values.

8.6.3.2 DNA analysis

After fully blinded genotyping has taken place, the results of the genotyping will be correlated with the salivary melatonin concentration, actigraphy results and clinical phenotype of the individuals. For the clinical phenotype outcomes, two approaches will be taken. Firstly, association with the primary outcome of the trial will be undertaken. Secondly, mutually exclusive subgroups will be defined (without reference to the genotyping results) with regard to a combination of the CSHQ, actigraphy and dim-light melatonin onset (DLMO) salivary sample results. The disorders most relevant to endogenous melatonin production will be Circadian rhythm sleep disorders (CRSD) either advanced, delayed or free-running.

8.7 Loss to Follow-up

If any of the trial patients are lost to follow up, contact will initially be attempted through the trial RP and the lead investigator at each Centre. If the lead investigator at the trial Centre is not the patient's usual clinician responsible for their speciality care then follow-up will also be attempted through this clinician. Where all of these attempts are unsuccessful, the child's GP and/or District Nurse will be asked to contact the family and provide follow-up information to the recruiting Centre. This information will be included on the patient information sheet.

8.8 Trial Closure

The end of the trial will be considered as the date of the final database lock; however the trial may be closed prematurely by the Trial Steering Committee, on the recommendation of the Data Monitoring Committee, for reasons such as clear differences between the safety of trial treatments.

9 STATISTICAL CONSIDERATIONS

9.1 Introduction

A separate and full statistical analysis plan will be developed prior to the analysis of the trial. The analysis plan will be agreed by the Trial Steering Committee before being sent to the Data Monitoring Committee for comment and approval.

9.2 Method of Randomisation

Randomisation lists will be generated in STATA using simple block randomisation with random variable block length. Randomisation will be stratified by centre.

9.3 Outcome Measures

9.3.1 Primary

1. Total night-time sleep (time from sleep onset to off-set, minus night awakenings)
   Data for this outcome will be taken from the sleep diaries. The sleep diary (Section 8.3.1) covers a period of one week and parents document their child's bed time, time they fall asleep and the final time that they wake up in the morning. The diary therefore allows parental perception* of their child's sleep periods to be documented. Total sleep time is calculated as the time from sleep onset to off-set minus any night awakenings.

   Total night-time sleep may also be calculated from the actigraph data and this will be done as a secondary outcome to be crosschecked with the sleep diary data.

*Sleep diary records parental perception of a child's sleep. Parents are not required to differentiate between periods where the child is actually asleep and periods where the child is awake but quiet e.g. not disturbing the rest of the household. Therefore parents do not have to stay awake to complete the sleep diary.
**'Snuggle down time' is defined as 'the time you stop other activities, and ask, suggest or encourage your child to settle down for sleep. For many children this will be when they lie down (usually in bed) and the lights are turned off or dimmed.'

A minimum of 5 out of 7 nights of sleep diary data is required for analysis. Week T-1W will be used as the baseline to be compared with week T+11W.

9.3.2 Secondary

1. Total night time sleep calculated using actigraphy data
2. Sleep efficiency calculated by (number of minutes spent sleeping in bed/total number of minutes spent in bed) x 100
3. Sleep onset latency (the time taken to fall asleep) calculated using actigraphy
4. Sleep onset latency (the time taken to fall asleep) calculated using sleep diaries
5. Composite sleep disturbance index scores
6. Daily global measure of parental perception of child's sleep quality
7. Behavioural problems assessed using Aberrant Behaviour Checklist (ABC)

8. Quality of Life of the parent assessed using the Family Impact Module of the PedsQL ™
9. Level of daytime sleepiness in caregivers assessed using Epworth Sleepiness Scale
10. Number and severity of seizures evaluated using seizure diaries throughout trial follow-up
11. Adverse effects of melatonin treatment assessed weekly between weeks T0W to T12W using 'TESS' (Treatment Emergent Signs and Symptoms) (Section 8.4.1)
12. Salivary melatonin concentrations
13. Associations between genetic variants and abnormal melatonin production.

*Sleep onset latency (time from bedtime until the start of sleep) calculated using actigraphy. Data for this outcome will be taken from the actigraph. Lights out/ snuggle down time** will be recorded by parents in the sleep diary. The start of sleep is defined using the actigraph as outlined in section 8.3.2. Sleep onset latency is calculated as the number of minutes between lights out/ snuggle down time and sleep onset.

9.4 Sample Size

Sample size calculations were undertaken using NQuery Advisor software version 4.0.

For the outcome 'total night-time sleep', the change between the total amount of sleep before randomisation and following randomisation will be calculated for each child. The titration period will not be used for the analysis of change. The null hypothesis is that there is no difference in the change over baseline in the total amount of sleep between the melatonin and placebo groups. The alternative hypothesis is that there is a difference in the change over baseline in the total amount of sleep. The study will be designed to detect a difference of one hour total sleep time in this change over baseline between the melatonin group and the placebo group. Assuming a common standard deviation of 1.7 (based on published data in similar populations/settings[3;13], a sample size of 47 per group, increasing to 57 per group to allow for estimated 20% loss to follow-up, will be required to provide 80% power using a t-test with a 0.05 two-sided significance level.

In the sample size calculation the difference to detect was deemed to be the minimum that would be beneficial to the child and their families. This was based on discussion with clinicians actively involved in the treatment of such children and discussion with affected families.

Table 4: Planned recruitment targets at each centre are:

Recruiting Centres	Target Accrual per centre	Recruiting Centres	Target Accrual per centre
Alder Hey Hospital	15	Derbyshire Children's Hospital	5
Royal Manchester Children's Hospital	10	Queens Medical Centre	5
Evelina Children's Hospital	17	John Radcliffe Hospital	14
University College Hospital London	12	Chesterfield Royal Hospital	8
Royal Devon and Exeter Hospital	6	Torbay Hospital	3

Birmingham Children's Hospital and Gulson Hospital	15	Bristol Royal Hospital for Children and Southmead Hospital	7
Queen Mary's Hospital	5	Victoria Blackpool Hospital	5
Arrowe Park Hospital	7	Leicester General Hospital	6
Southampton General Hospital	12	Sheffield Children's Hospital	6
University Hospital of Wales	8	Northampton General Hospital (this centre was never initiated and IMP was re-distributed to other centres)	0

N.B. Northampton was never initiated as a centre. Although centre targets remained unchanged, the packs of IMP allocated to Northampton were re-distributed between Manchester, Blackpool and UCLH to enable continued recruitment.

The final follow up should be completed 12 weeks after randomisation of the last participant and statistical analysis will begin immediately after this time point following the closure of the database for data entry.

9.5 Interim Monitoring and Analyses

The estimates of the common standard deviations used in the sample size calculation will be checked after the first 30 participants have been randomised and completed follow-up. This blinded internal pilot is not deemed to have any significant impact on the final analysis. If the standard deviation is smaller than that used in the sample size calculation, suggesting that fewer patients were required than initially proposed, then no action will be taken and the size of the study will remain as planned. If the standard deviation is larger than assumed suggesting the need for more patients then on the advice of the Data Monitoring Committee, the Trial Steering Committee will aim to increase recruitment and consider implications for funding and existing resources.

Missing data will be monitored and strategies developed to minimise its occurrence, however as much data as possible will be collected about the reasons for missing data and this will be used to inform any imputation approaches employed.

9.6 Analysis Plan

The study will be analysed and reported following the 'CONSORT' guidelines (Consolidated Standard of Reporting Trials)[38-41].
Data from all the study children will be analysed on completion of the study (T12W) on an intention to treat basis.
All analyses will be pre-specified in detail in the statistical analysis plan and agreed by both the Trial Steering Committee and the Data Monitoring Committee prior to the internal pilot.
Missing data will be handled by considering the robustness of the complete case analysis to sensitivity analyses using various imputation assumptions; however these will be informed by data collected on the reasons for missing data.

9.6.1 Sub-study Data Analysis

Statistical methodology for investigating genetic associations is a field that is developing at a rapid pace; however there is not as yet consensus as to the most effective methods. Traditional methodologies alone are not sufficient to deal with the complexities associated with the modelling of relationships between genetic profile and outcome, and the lack of success reported by reviewers of recent association studies is in part due to inadequate statistical analysis. The most up to date statistical

methods will be applied to the data in order to extract the maximum information possible.

Prior to the association analyses, a test for Hardy-Weinberg Equilibrium (HWE) will be undertaken at each SNP genotyped. Any marker found to deviate significantly from HWE (after accounting for multiple testing) will be excluded from the analyses. However, the reason for the deviation e.g. population substructure or genotyping error will be investigated. Population substructure will also be tested for by genotyping a minimum of 20 additional SNPs known to be independent of the SNPs of interest[42]. SNPs found to have minor allele frequency of less than 1% will also be excluded from the analyses.

In order to capture putative SNPs not on the 370k chip, a data imputation method such as that described by Marchini et. al.[45] will be used to impute genotype data for the SNPs not included on the chip. These imputed genotypes will be tested for association in exactly the same way as the SNPs actually genotyped.

For the purpose of analysing the outcomes of interest, univariate analyses will first of all be undertaken to test for association with each SNP. The chi-squared or Fisher's exact test will be used for binary outcomes as appropriate, ANOVA will be used for continuous outcomes and the log-rank test will be used for time to event outcomes. Due to the huge number of SNPs being genotyped, multiple testing is obviously a key issue and so in addition to the p-values resulting from the univariate tests for association, a Bayes' Factor[46] will also be calculated to assess the strength of the evidence of association. A priori weights, calculated with reference to factors such as functional knowledge and linkage disequilibrium information will be applied to the Bayes' factor in order to reflect the relative weight of evidence attached to each SNP.

The univariate analyses will be followed by multiple regression analyses where regression models will be built for each gene separately. Logistic regression will be used for binary outcomes, linear regression will be used for continuous outcomes and proportional hazard models (with the assumption of proportional hazards being validated) will be used for time to event outcomes. Finally, regression models for each chromosome will be built, to include covariates representing SNPs within each gene found to be statistically significant in the per-gene analyses. If it is felt necessary due to the substantial number of SNPs contributing to each regression model, prior to building the models an assessment of the extent of linkage disequilibrium (LD) between the individual SNPs will be made and only one SNP from any group of SNPs found to be in strong LD will be included in the models in order to reduce the problems of collinearity and model overfitting. Backward selection will also be applied to the regression models to reduce these problems further. The models will initially include covariates to represent SNP main effects only, however once main effects are found to be statistically significant, SNP-SNP and SNP-environment interaction terms will be introduced into the models and tested for significance.

In all analyses, additive genetic effects will be assumed in the first instance. However, for the SNPs found to have a significant effect on outcome, dominant effects will then be added to the regression models to assess whether they have any additional effect.

If it is deemed appropriate, the above traditional regression methods will be supplemented with more recently developed statistical methods used specifically in genetic association studies.

10 PHARMACOVIGILANCE

10.1 Terms and Definitions

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

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

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

Unexpected Adverse Reaction (UAR)
An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question set out in the investigator's brochure.

Serious Adverse Event (SAE), Serious Adverse Reaction (SAR) or Suspected Unexpected Serious Adverse Reaction (SUSAR)
Any adverse event, adverse reaction or unexpected adverse reaction, respectively, that:

- results in death
- is life-threatening* (subject at immediate risk of death)
- requires in-patient hospitalisation or prolongation of existing hospitalisation**
- results in persistent or significant disability or incapacity, or
- consists of a congenital anomaly or birth defect
- other important medical events

*'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
**Hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisations for a pre-existing condition, including elective procedures that have not worsened, do not constitute an SAE.
Other important medical events that may not result in death, be life-threatening, or require hospitalisation may be considered a serious adverse event/experience when, based upon appropriate medical judgment, they may jeopardise the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

10.2 Notes on Adverse Event Inclusions and Exclusions

10.2.1 Include

- An exacerbation of a pre-existing illness
- An increase in frequency or intensity of a pre-existing episodic event/condition

- A condition (even though it may have been present prior to the start of the trial) detected after trial drug administration
- Continuous persistent disease or symptoms present at baseline that worsens following the administration of the study/trial treatment
- Treatment Emergent Signs and Symptoms (TESS) evaluation, to include the following specific signs and symptoms:
    - somnolence
    - increased excitability
    - mood swings
    - seizures (new presentation or exacerbation)*
    - rash
    - hypothermia
    - cough
    - other adverse effects not listed will also be documented; the Investigator's Brochure should be referred to when assessing causality and expectedness.

*A seizure diary will be given to the parents of those children who have an established diagnosis of epilepsy, whether or not they are receiving any antiepileptic medication (see Section 8.4.2).
Signs and symptoms will be graded and reported as; no symptoms (score 0); mild symptoms (score 1); moderate symptoms (score 2) and severe symptoms (score 3). Seriousness and causality will also be assessed by the reporting researcher (see section 10.3).

10.2.2 Do Not Include

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

10.3 Severity / Grading of Adverse Events

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

Mild: does not interfere with routine activities
Moderate: interferes with routine activities
Severe: impossible to perform routine activities
A distinction is drawn between serious and severe AEs. Severity is a measure of intensity (see above) whereas seriousness is defined using the criteria in section 10.1, hence, a severe AE need not necessarily be a Serious Adverse Event.

10.4 Relationship to Trial Treatment

The assignment of the causality should be made by the investigator responsible for the care of the participant using the definitions in table 5.

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

Table 5: Definitions of Causality

Relationship	Description
Unrelated	There is no evidence of any causal relationship. *N.B. An alternative cause for the AE should be given*
Unlikely	There is little evidence to suggest there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).
Possibly	There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).
Probably	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
Almost certainly	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.

10.5 Expectedness

An AE whose causal relationship to the study drug is assessed by the investigator as "possible", "probable", or "almost certain" is an Adverse Drug Reaction.
All events judged by the investigator to be possibly, probably, or almost certainly related to the IMP, graded as serious and **unexpected** (see section 10.2 for list of Expected Adverse Events) should be reported as a SUSAR.

10.6 Follow-up After Adverse Events

All adverse events should be followed until satisfactory resolution or until the investigator responsible for the care of the participant deems the event to be chronic or the patient to be stable.
When reporting SAEs and SUSARs the investigator responsible for the care of the participant should apply the following criteria to provide information relating to event outcomes: resolved; resolved with sequelae (specifying with additional narrative; not resolved/ongoing; ongoing at final followup; fatal or unknown.

10.7 Reporting Procedures

All adverse events should be reported. Depending on the nature of the event the reporting procedures below should be followed. Any questions concerning adverse event reporting should be directed to the MCRN CTU in the first instance. A flowchart is given below to aid in determining reporting requirements.

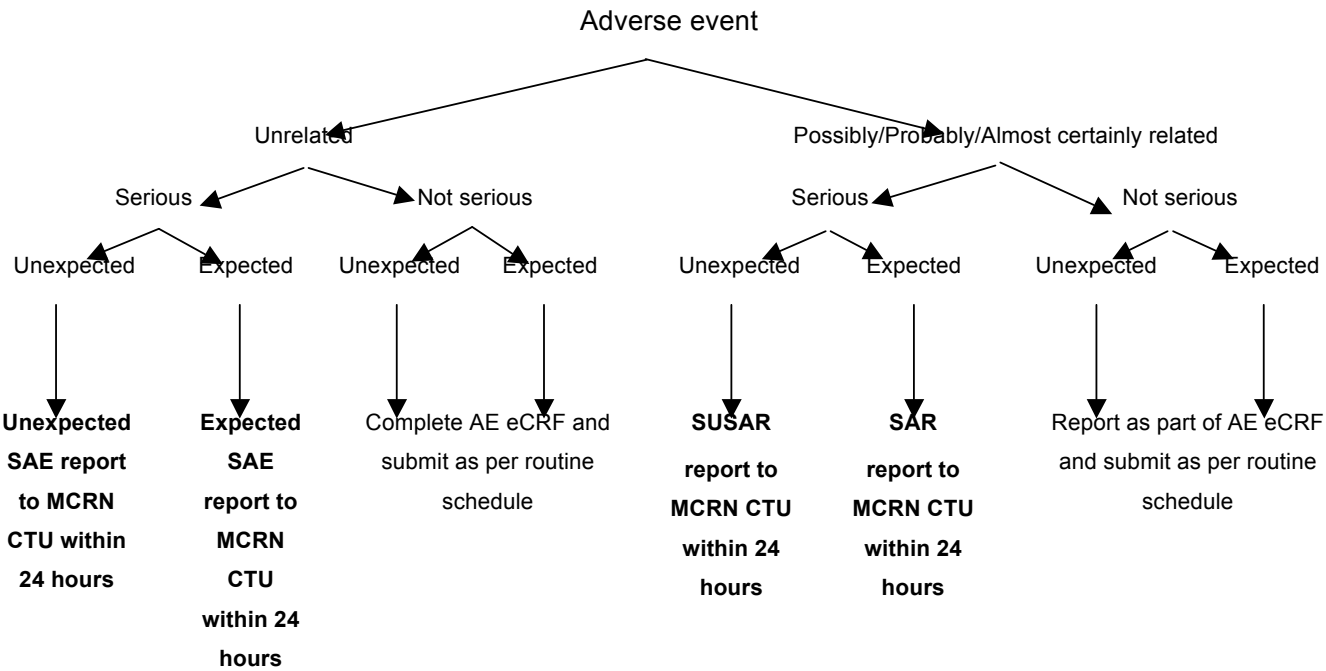
10.7.1 Non serious ARs/AEs

All such events, whether expected or not, should be recorded on an Adverse Event eForm on the laptop. This laptop must then be connected to the Internet to ensure

that this data is transmitted to the MCRN CTU within seven days of the form being due.

10.7.2 Serious ARs/AEs/SUSARs

SARs, SAEs and SUSARs should be reported within 24 hours of the local site becoming aware of the event. The electronic SAE form asks for the nature of event, date of onset, severity, corrective therapies given, outcome and causality. The responsible investigator should sign (electronic signature) the causality of the event. The RP will need to connect their laptop to the server within 24 hours of becoming aware of the event in order to upload the information to the MCRN CTU. Daily reports will be generated from the eCRFs and will be checked daily by the Trial Co-ordinator via the Trial Management System. The local site should send any additional information within 5 days if the reaction has not resolved at the time of reporting.
The MCRN CTU will notify the MHRA and main REC of all SUSARs occurring during the study according to the following timelines; fatal and life-threatening within 7 days of notification and non-life threatening within 15 days. All investigators will be informed of all SUSARs occurring throughout the study. Local investigators should report any SUSARs and /or SAEs as required by their Local Research Ethics Committee and/or Research & and Development Office.



10.8 Responsibilities - Investigator

The Investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to study product.
All SAEs must be reported within 24 hours by the investigator to the MCRN CTU on an SAE form unless the SAE is specified in the protocol or IB as not requiring immediate reporting. All other adverse events should be reported on the regular progress/follow-up reports.

Minimum information required for reporting:

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

i. The SAE eForm should be completed by the responsible investigator, the consultant named on the 'signature list and delegation of responsibilities log' who is responsible for the patient's care. The investigator should assess the SAE for the likelihood that that it is a response to an investigational medicine. In the absence of the responsible investigator the form should be completed and signed (digitally) by a designated member of the site trial team and submitted to the MCRN CTU. The responsible investigator should check the SAE form, make changes as appropriate, sign and then re-send to the MCRN CTU as soon as possible. The initial report shall be followed by detailed reports as appropriate.
ii. Staff at the institution must **notify** their local ethics committee (LREC) and their R and D department of the event (as per standard local procedure).
iii. In the case of an SAE the individual must be followed-up until clinical recovery is complete and laboratory results have returned to normal, or until the event has stabilised. Follow-up may continue after completion of protocol treatment if necessary.
iv. Follow-up information is noted on another SAE eForm and submitted to the MCRN CTU as information becomes available. Extra, annotated information and/or copies of test results may be provided separately.
v. The patient **must** be identified by randomisation number, date of birth and initials only. The patient's name **should not** be used on any correspondence.

10.8.1 Maintenance of Blinding

Systems for SUSAR and SAR reporting should, as far as possible, maintain blinding of individual clinicians and of trials staff involved in the day-to-day running of the trial. Unblinding clinicians may be unavoidable if the information is necessary for the medical management of particular patients. The safety of patients in the trial always takes priority. Seriousness, causality and expectedness should be evaluated as though the patient was on active drug. Cases that are considered serious, unexpected and possibly, probably or almost certainly related (i.e. possible SUSARs) would have to be unblinded at the clinical trials unit. Only those events occurring among patients on the active drug (unless thought to be due to the excipient in the

placebo) should be considered to be SUSARs requiring reporting to the regulatory authority and ethics committee.

10.9 Responsibilities – MCRN CTU

The MCRN CTU is undertaking duties delegated to them by the trial sponsor, The Alder Hey Children's NHS Foundation Trust, and is responsible for the reporting of SUSARs and other SARs to the regulatory authorities (MHRA, competent authorities of other European member states in which the trial is taking place and, if required, the research ethics committees) as follows:

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

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

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

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

The MCRN CTU will also send an annual safety report containing a list of all SARs to regulatory authorities and MREC. Copies of the report will be sent to the Principal Investigator at all institutions participating in the trial and to Alliance Pharmaceuticals for their information.

Alliance reports to be sent to:
Pharmacovigilance
Alliance Pharmaceuticals
Avonbridge House
Bath Road
Chippenham
Wilts SN15 2BB
Tel: 01249 466966
Fax : 01249 466977
Email: pharmacovigilance@alliancepharma.co.uk
Out of hours pager 07699 728828

Patient safety incidents that take place in the course of research should be reported to the National Patient Safety Agency (NPSA) by each participating NHS Trust in accordance with local reporting procedures.

10.9.1 Reporting of Pregnancy

Any pregnancy, which occurs during the study, should be reported to the MCRN CTU and the individual must be instructed to stop taking study drugs. All pregnancies that occur during treatment or within 90 days of completing treatment need to be followed up until conclusion and reported separately.
The investigator should counsel the patient; discuss the risks of continuing with the pregnancy and the possible effects in the foetus. Appropriate obstetric care should be arranged. Pregnancy occurring in the partner of an individual participating in the study should also be reported to the investigator and the MCRN CTU. The partner should be counselled and followed as described above.

11 ETHICAL CONSIDERATIONS

11.1 Ethical Considerations

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

We consider the specific ethical issues relating to participation in this trial to be:

- Taking a placebo (dummy) treatment or the active (melatonin) treatment; there is no other single, 'gold standard' drug that is used to treat disturbed sleep in children. Those drugs that are prescribed have obvious and unpleasant side-effects, making blinding impossible. Placebo is therefore an appropriate comparator because it avoids unnecessary exposure of trial participants to potential adverse effects from an active comparator, whilst double-blinding enables the true treatment effect of melatonin to be investigated.
- Pregnancy testing; we do not anticipate that this will be required for many, if any, patients eligible for this trial. There is a theoretical risk relating to the use of melatonin during pregnancy or lactation but data to support this is scarce. We believe it is in the interest of patient safety to classify pregnancy as an exclusion criteria, however do not consider that a pregnancy test should be a mandatory requirement. This being the case we must establish that those girls or young women who are sexually active are counselled about the potential risks and offered to undergo pregnancy screening. Refusal to undertake a pregnancy test will not preclude entry into the trial.
- Wearing a piece of medical equipment (the Actigraph); the instruments to be used are similar in shape and size to a wristwatch and are worn on the wrist in the same way. The Actigraph is worn next to the skin (as a wristwatch would be) and will not interfere with skin integrity. There are no wires attached to restrict movement.
- Additional test; salivary melatonin assay at T-1W (i.e. the evening prior to the T0 clinic visit) and T+10W. This test is not performed routinely in clinical practice, however it will enable accurate categorisation of those children who are physiologically phase delayed at the beginning of the study, which may prove to be an important consideration when comparing responders to non-responders. Although the test will be offered to all children at T-1W it is our estimate that around 75% will be able to comply. Those unable to comply at T-1W will not be re-tested at T+10W. To maintain anonymity samples will be labelled with unique identifiers only.
- The ability to detect genetic variations that account for abnormal melatonin production has been described by the Human Genetics and Cognitive Functions laboratory at the Pasteur Institute, France. Collection of DNA from MENDS trial participants will enable us to explore the association between genetic variants and abnormal melatonin production and its subsequent association with sleep disorder. The genetic sub-study will be subject to a separate consent process (using a separate information sheet) to the main study and participants will be able to refuse participation in this but still take part in the main study
- Case Report Forms in English only; to provide appropriate translations of trial documentation will require checks and validations of language, as well as a comprehensive review of cultural influences upon sleep hygiene. We unfortunately do not have the resources to adequately fulfil these standards and therefore must limit trial entry to English speakers.

11.2 Ethical Approval

The trial protocol and all substantial amendments will be submitted for review by the North West Multi-centre Research Ethics Committee (MREC) and each centre must undergo Site Specific Assessment (SSA) by the relevant Local Ethical Research Committee (LREC).

The CTU should receive notification of positive SSA for each new centre via the MREC: usually this will be through the CI. A copy of local Research & Development (R&D) approval and of the Patient Information and Consent Form, on local headed paper, should be forwarded to MCRN CTU before patients are entered.

11.3 Informed Consent Process

11.3.1 General

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

Potential participants will generally be identified by community paediatricians, who would routinely refer to specialist centres for review of sleep disorders. The community paediatricians will provide potential participants with written information about the trial, including contact details of the research team should they require further information, and arrange for an out patient clinic appointment in the usual way.

Parental and age-and-stage-of-development appropriate Patient Information and Consent forms (PIC), approved by an independent ethical committee (IEC), will be issued by the community paediatrician. The PIC will describe in detail the trial procedures (both the sleep hygiene and treatment phases), the interventions/products, and potential risks/benefits. All patients and their parent/legal representative will receive the appropriate version of the written information and be asked to read and review it. The PIC will emphasise that participation in the trial is voluntary and that the parent or legal representative may, without the minor being subject to any resulting detriment, withdraw the minor from the trial at any time by revoking the informed consent. The rights and welfare of the patients will be protected by emphasising to them that the quality of medical care will not be adversely affected if they decline to participate in this study. All parents/legally acceptable representatives and patients will be given the opportunity to ask questions and will be given sufficient time to consider trial entry before consenting.

The consent form will request permission for the patient's General Practitioner to be informed of their involvement in the trial and also permission for personnel involved in the research or from regulatory authorities to have access to the individual's medical records.

11.3.2 Process of Informed Consent

11.3.2.1 Prior to Trial Registration

The consent process at this stage will be carried out by a member of the research team identified in the trial signature and delegation log. Discussion of objectives and potential inconveniences of the four week sleep hygiene intervention period, and the conditions under which it is to be conducted, are to be provided to patients by staff

with experience with minors. Both parental consent and, if appropriate, the patients assent will be obtained **prior** to any study related procedure being carried out.
Both the researcher taking consent and the parent* or legally acceptable representative of the minor must personally sign and date the form. If capable, the patient should assent and sign and personally date a separate IEC-approved assent form; this form should also be signed and dated by the parent or legal representative. Assent forms do not substitute for the consent form signed by the patient's legally acceptable representative. Where the child is unable to provide assent, this should be documented in the patient's medical notes, and recorded on the age and stage of development specific PISC. The original copy of the signed consent/assent forms will be retained in the child's medical notes and must be made available for inspection. A copy will be returned to the MCRN CTU and one will also be put in the investigator site file. A further copy of the signed consent/assent forms will be given to the child's parent/legal representative (Appendix B).
*Legally this includes married parents or unmarried mothers, unmarried fathers cannot consent without a court order granting them parental responsibility.

11.3.2.2 Prior to Randomisation

The consent process at T0W must be carried out by a medically qualified member of the research team identified in the signature and delegation log. Discussion of objectives, risks and inconveniences of the trial and the conditions under which it is to be conducted are to be provided to patients by staff with experience with minors. Both parental consent and, if appropriate, the patients assent should be obtained **prior** to any study related procedure being carried out.
All patients undertaking the four week sleep hygiene interval, and their parent/legal representative, will have received an appropriate version of the IEC-approved written information prior to consenting to enter the sleep hygiene intervention period. At the next clinic visit following completion of the sleep hygiene intervention, individuals will be re-screened to consider eligibility to enter the treatment phase of the MENDS trial. The investigator will reiterate previous written and verbal explanations about the research study to the patient and their parent/legal representative and answer any questions that may arise.
The patient and their parent/legal representative will have had the opportunity to discuss the study with their surrogates and think about it prior to agreeing to participate. Both the clinician taking consent and the parent/legal representative of the patient must personally sign and date the form.
If capable, the patient should assent and sign and personally date a separate IEC-approved assent form, describing (in simplified terms) the details of the trial intervention/product, trial procedures and risks. The parent or legal representative should also sign and date the assent form. Assent forms do not substitute for the consent form signed by the patient's legally acceptable representative. Where the child is unable to provide assent, this should be documented in the patient's medical notes, and recorded on the age and stage of development specific PISC.
The original copy of the signed consent/assent forms will be retained in the child's medical notes and must be made available for inspection. A copy will be returned to the MCRN CTU and one will also be put in the investigator site file. A further copy of the signed consent/assent forms will be given to the child's parent/legal representative (Appendix B).

11.3.2.3 Prior to Collection of DNA

Consent for obtaining DNA in the form of a salivary sample will generally be obtained at the T-2W home visit. The consent process at this stage will therefore be carried out by the research practitioner identified in the trial signature and delegation log.

An IEC approved parental and age-and-stage-of-development appropriate PIC, specifically designed for the sub-study (Appendix B) will be issued at the T-4W clinic visit. Discussion of objectives and potential inconveniences of participating in the sub-study are to be provided to patients by staff with experience with minors. Both parental consent and, if appropriate, the patients assent will be obtained **prior** to collection of the DNA sample and completion of the SCQ questionnaire.
Both the research practitioner taking consent and the parent or legally acceptable representative must personally sign and date the form. If capable, the patient should assent and sign and personally date a separate IEC-approved assent form. The parent or legal representative should also sign and date the assent form. Assent forms do not substitute for the consent form signed by the patient's legally acceptable representative. Where the child is unable to provide assent, this should be documented in the patient's medical notes, and recorded on the age and stage of development specific PISC. The original copy of the signed consent/assent forms will be retained in the child's medical notes and must be made available for inspection. A copy will be returned to the MCRN CTU and one will also be put in the investigator site file. A further copy of the signed consent/assent forms will be given to the child's legal representative.

11.4 Study Discontinuation

In the event that the study is discontinued, children will be reverted to usual standard clinical care. Patients withdrawing early from trial treatment will also be reverted to normal standard care but will not be unblinded unless protocol unblinding criteria are fulfilled (see Section 7.5). If there is perceived benefit to the trial medication, children who withdraw from the trial may be offered melatonin outside of trial at the discretion of the clinician responsible for their usual clinical care.

12 REGULATORY APPROVAL

This trial has a Clinical Trial Authorisation (CTA), issued by the Medicines and Health Care products Regulatory Agency. The EudraCT reference is 2006-004025-28. All substantial amendments will be submitted to the MHRA as well as the MREC.

13 TRIAL MONITORING

13.1 Risk Assessment

In accordance with the MCRN CTU Standard Operating Procedure this trial has undergone a risk assessment, completed in partnership between the University of Liverpool, MCRN CTU, trial sponsor and co-lead investigators. In conducting this risk assessment, the contributors considered potential patient, organisational and study hazards, the likelihood of their occurrence and resulting impact should they occur.
The outcome of the risk assessment is expressed as a percentage, assigned according to the following categories:
Score ≤ 33% = Low risk
Score ≥34 to ≤ 67% = Moderate risk
Score ≥ 68 to ≤ 100% = High risk
The outcome of the MENDS trial risk assessment was a score of **16%** therefore it has been judged to be a **low risk** clinical trial.

13.2 Source Documents

Source data*: All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies). (ICH E6, 1.51).*
Source documents*: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial). (ICH E6, 1.52).*
In order to resolve possible discrepancies between information appearing in the eCRF and any other patient related documents, it is important to know what constitutes the source document and therefore the source data for all information in the eCRF. The following data recorded in the eCRF should be consistent and verifiable with source data in source documents *other* than the eCRF (eg medical record, laboratory reports and nurses' notes). If eCRF are also used in a hospital it should be ensured that these are used in compliance with GCP.

The following parameters that will be documented in the eCRFs are not source data:
Relevant medical history and diagnosis (medical notes are source documents)
Physical examinations and vital signs (medical notes are source documents)
Data obtained from sleep, quality of life and cognitive questionnaires (paper questionnaires are source documents)
Data obtained from sleep and seizure diaries (paper sleep and seizure diaries are source documents)

These parameters will be marked  in the eCRF.

Source documents for  marked sections in the eCRF should be identified prior to the clinical phase of the trial for each participating trial site.
Therefore, for data where no prior record exists and which is recorded directly in the eCRF, e.g. inclusion/exclusion criteria and adverse events, the eCRF will be considered the **source document**, unless otherwise indicated by the investigator. For remaining data, where no prior record exists and which is recorded directly in the paper CRF e.g., sleep diary, seizure diary, quality of life and cognitive evaluations,

the paper Case Report Form will be considered the **source document**, unless otherwise indicated by the investigator. All such exemptions should be identified prior to the clinical phase of the trial.
In addition to the above, date(s) of conducting informed consent and assent process including date of provision of patient information, registration number, randomisation number and the fact that the patient is participating in a clinical trial including treatment arms of melatonin and placebo therapy should be added to the patient's medical record chronologically, i.e. when treatment is allocated to the patient. Further, study treatment allocation should also be noted in the patient's medical record after unblinding of the study (see Section 7.5.3).

13.3 Data Capture Methods

Trial data will be captured using a combination of electronic and paper case report forms.

13.3.1 Electronic Case Report Forms

All of the Electronic Case Report Forms are accessed via a client application on each laptop computer. Each laptop will have access to a database of patients for a specific site. The client application is secured with a unique username/password combination allocated to each research practitioner. The eCRFs are available on a timeline system, where the necessary forms become active when they are needed. When data is entered into an eCRF it is stamped with the date, time and the person who entered it. If data is changed on an eCRF, it is stamped with date, time, person and a reason for change. The previous value is recorded in an audit trail for each data item. Data entered into each eCRF is uploaded securely (using Secure Socket Layer) to the main CTU database server each time the laptop is connected to the Internet. Each eCRF contains specific validation checks on the data being entered. If any values are outside what is expected, or data is missing, this is flagged up and will be raised as a discrepancy on the main database system. Weekly reports will identify discrepancies in the data, and allow for follow up.
Screening logs should be maintained and submitted weekly to the MCRN CTU. Registration and Randomisation eCRFs should be submitted to the MCRN CTU with 24 hours of patients being registered or randomised onto the study. All other routine eCRFs, results of electronic vigilance tests and actigraph data should be completed and submitted to the trial database within 7 days of study visit occurring.
SAEs, SARs and SUSARs should be reported as detailed in section 10.

13.3.2 Paper Case Report Forms

Sleep and seizure diaries will be completed by parents/guardians as paper records. The RP will collect the completed proformas, check them for completeness and query omissions. The RP should retain a copy of these CRFs and return the original to the MCRN CTU within 7 days of study visit occurring.
The other questionnaires will be completed by the parent or RP (as applicable); the RP will calculate the scores and enter them into the eCRF. The RP should retain a copy of these CRFs and return the original to the MCRN CTU within 7 days of study visit occurring.

13.4 Monitoring at CTU

The MCRN CTU will review recruitment rates, withdrawals and losses to follow-up and identified problems will be reviewed by the TMG and remedial action taken as necessary. Data submitted to the database will be centrally monitored by the CTU to

ensure that data collected are consistent with adherence to the trial protocol. Data will be checked for missing or unusual values (range checks) and checked for consistency within participants over time. Discrepancies that have been raised can be queried, and resolved at the CTU, or by the remote RP. Each discrepancy will keep a complete log of what data has been changed, the time of each change, and the person who changed it.

13.5 Clinical Site Monitoring

13.5.1 Direct Access to Data

Site monitoring may be deemed to be necessary as a result of central data checks. In order to perform their role effectively, the trial coordinator (or monitor) and persons involved in Quality Assurance and Inspection may need direct access to primary data, eg patient records, laboratory reports, appointment books, etc. Since this affects the patient's confidentiality, this fact is included on the Patient Information Sheet and Informed Consent Form.

13.5.2 Confidentiality

Individual participant medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below.

Electronic and paper CRFs will be labelled with patient initials and unique trial registration and/or randomisation number. Saliva and DNA samples will be transferred to external laboratories and will be identified by unique identifiers only.

Medical information may be given to the participant's medical team and all appropriate medical personnel responsible for the participant's welfare.

Verification of appropriate informed consent will be enabled by the provision of copies of participants' signed informed consent/assent forms being supplied to the MCRN CTU by recruiting centres. This requires that name data will be transferred to the MCRN CTU, which is disclosed in the PIC. The MCRN CTU will preserve the confidentiality of participants taking part in the study and The University of Liverpool is registered under the Data Protection Act.

13.5.3 Quality Assurance and Quality Control of Data

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

- The Principal Investigator, Research Practitioner and designated Pharmacist from each centre will attend the trial launch meeting, coordinated by CTU in conjunction with co-lead investigators, Dr Richard Appleton and Dr Paul Gringras, which will incorporate elements of trial- specific training necessary to fulfil the requirements of the protocol
- The Trial Coordinator is to verify appropriate approvals in place prior to initiation of a site and the relevant personnel have attended trial specific training
- The Trial Coordinator is to check safety reporting rates between centres

- The Trial Coordinator is to monitor screening, recruitment and drop-out rates between centres
- The Trial Coordinator is to conduct data entry consistency checks and follow-up data queries
- Independent oversight of the trial will be provided by the Data Monitoring Committee and independent members of the Trial Steering Committee

13.6 Records Retention

The investigator at each investigational site must make arrangements to store the essential trial documents, including the Investigator Site File, until the MCRN CTU informs the investigator that the documents are no longer to be retained, or for a maximum of 15 years, whichever is soonest.

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

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

The MCRN Clinical Trials Unit undertakes to store originally completed CRFs and separate copies of the above documents for the same period, except for source documents pertaining to the individual investigational site, which are kept by the investigator only.

14 INDEMNITY

MENDS is sponsored by the Alder Hey Children's NHS Foundation Trust, and co-ordinated by the MCRN CTU in the University of Liverpool. As this is an investigator-initiated study, The Association of the British Pharmaceutical Industry (ABPI) guidelines for patient compensation by the pharmaceutical industry do not apply.
Alder Hey Children's NHS Foundation Trust shall provide an indemnity in respect of Clinical Negligence to the extent that such an indemnity is permitted by the NHS Litigation Authority's Clinical Negligence Scheme for Trusts.

For the purposes the study Clinical Negligence is defined as:-

"A breach of duty of care by members of the health care professions employed by NHS bodies or by others consequent on decisions or judgments made by members of those professions acting in their professional capacity in the course of their employment, and which are admitted as negligent by the employer or are determined as such through the legal process." (NHS Indemnity: Arrangements for Clinical Negligence Claims in the NHS (October 1996.))

15 FINANCIAL ARRANGEMENTS

This study is funded by the Health Technology Assessment programme (HTA) of the Department of Health. Contractual agreements will be in place between sponsor and collaborating sites that will incorporate financial arrangements.

15.1 Participant Payments

Participants and their parents/guardians will not be paid to participate in the trial. The schedule of study visits is in line with routine standard care. Additional visits are avoided by the provision of research practitioners who will perform home visits to conduct trial-related assessments.

15.2 Stationary

A sum of £300 per collaborating site is allocated for provision of general office supplies; paper, site files, photocopying/printing, envelopes, telephone.

15.3 Pharmacy Department

The randomisation service for the trial will be provided by the pharmacy department in each of the ten collaborating sites. Provision of payment to support pharmacy costs (setup, storage, dispensing, reconciliation and GCP quality assurance), totalling £500 per participating site, has been allocated.

16 TRIAL COMMITTEES

16.1 Trial Management Group (TMG)

The Trial Management Group (TMG) will comprise Dr Richard Appleton, Dr Paul Gringras, Prof Paula Williamson, Dr Carrol Gamble, Mr Ashley Jones, Miss Charlotte Stockton and pharmacy representative Ms Catrin Barker, and collaborating investigators; Dr Paul Montgomery, Dr Luci Wiggs and Dr Alastair Sutcliffe. The TMG will be responsible for the day-to-day running and management of the trial and will meet approximately 3 times a year.

16.2 Trial Steering Committee (TSC)

The Trial Steering Committee will consist of an independent chairperson, Professor Stuart Logan, Professor of Paediatric Epidemiology, Peninsula Medical School, and 2 additional independent members; Mr Andy Vail providing statistical expertise and Dr Tony McShane, a paediatric neurologist. Additional members will comprise co-applicants and collaborators; Mrs Ann Whittle (consumer), Dr Richard Appleton, Dr Paul Gringras, Prof Alan Emond, Prof Paula Williamson, Dr Carrol Gamble, Mr Ashley Jones, Dr Megan Thomas and Miss Charlotte Stockton. The role of the TSC is to provide overall supervision for the trial and provide advice through its independent Chairman. The ultimate decision for the continuation of the trial lies with the TSC. The TSC will receive reports from the DMC and will convene shortly after each meeting of the DMC.

16.3 Data Monitoring Committee (DMC)

The Data Monitoring Committee (DMC), also known as the Data Monitoring and Ethics Committee (DMEC), comprises 3 independent members; Professor David Jones, (Prof of Medical Statistics; Biostatistics and Genetic Epidemiology Research Theme Leader, University of Leicester), Dr John Gibbs (Consultant Paediatrician, Countess of Chester Hospital, who has expertise in paediatric neurological and neuro-developmental disorders) and Prof Tony Marson, Consultant Neurologist, Walton Centre for Neurology & Neurosurgery, an experienced clinician and trialist.

The DMC will be responsible for reviewing and assessing recruitment, interim monitoring of safety and effectiveness, trial conduct and external data (further information is provided in the DMC Charter). The DMC will first convene prior to trial initiation. They will establish the DMC chairperson at this time and will then define frequency of subsequent meetings (at least annually). Details of the interim analysis and monitoring are provided in section 9.

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

17 PUBLICATION

The results from different centres will be analysed together and published as soon as possible after the close of the trial. Individual clinicians must undertake not to submit any part of their individual data for publication without the prior consent of the Trial Management Group.

The Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://www.icmje.org/) and the CONSORT guidelines[43] will be respected. The ISRCTN allocated to this trial should be attached to any publications resulting from this trial.

BMJ guidance on authorship and contributorship (see http://bmj.com/advice/3.html) will be use to acknowledge the level and nature of contribution of key individuals in publications arising from the trial. The publication strategy shall lie under the jurisdiction of the Trial Steering Committee.

18 PROTOCOL AMENDMENTS

18.1 Version 7.0 (01/04/2010)

Seventh Substantial amendment Version 6.2 23/06/2009 to Version 7.0 01/04/2010

Page No.	Comment
Throughout	Updated version and date; updated cross-referencing to sub-sections and page numbers where appropriate and updated Sponsor's name and email address (formerly known as Royal Liverpool Children's NHS Trust – now known as Alder Hey Children's NHS Foundation Trust).
Throughout	Removed all references to Royal Liverpool Children's Hospital (RLCH) as this is now known as Alder Hey Hospital. 4, 5, 22, 70,83 Updated email address for Trial Co-ordinator, and Chief Investigator and job titles for Statistics Team Leader, Trial Statistician and DMC Chair.
22 & 83	Updated address for Royal Manchester Children's Hospital.
10, 18, 48-50	Changes to Statistical Considerations, namely sample size calculation and recruitment target.
10, 18, 48-50	Sleep onset latency (SOL) calculated using actigraphy has been moved from a primary to a secondary outcome. SOL calculated using sleep diaries has been added as a secondary outcome.
14	Sleep onset latency has been removed from the Objective of the Trial.
22, 23, 84, 86	Removed GOSH and Northampton from lists of pharmacies and centres as these centres were never initiated.
7, 37, 39, 45	References to Epworth Sleepiness Scale put back into their original locations in the protocol. In the previous substantial amendment, the removal of the Epworth Sleepiness Scale was described in the substantial amendment form in error. There was never an intention to remove the scale which has been used throughout the trial.
49	Targets for centres updated.

Substantial amendment Version 6.1 04/03/2009 to Version 6.2 10/07/2009.

Page No.	Comment
Throughout	Updated version and date; updated cross-referencing to sub-sections and references
4, 21, 69	Change to the Trial Co-ordinator - Charlotte Stockton has replaced Joanne Milton as the trial co-ordinator.
5 & 69	Dr Megan Thomas is no longer and independent member of the Trial Steering Committe (TSC), but she remains a non-independent member of the TSC.
11	Amendment of text in trial summary and figure 1 to reduce the age of inclusion to 3 years.
18	Reduction in age of inclusion to three years at the time of registration. A number of sites have raised the age of inclusion as a barrier to recruitment as children with severe sleep problems have often been prescribed melatonin before the age of five. We expect this amendment to increase the number of registrations by approximately twenty percent. The decision has been made not to produce a patient information sheet specifically for the three to five age range, particularly as children in the MENDS trial have moderate to severe

	developmental delay. If a child under five is considered to have sufficient understanding they can be provided with the patient information sheet for the five to ten age group for their care-giver to read to them. An Adaptive Behaviour Assessment System (ABAS) questionnaire is available for this age group to confirm developmental delay. The cut-off for inclusion into the trial will remain as a percentile rank below 7. The drug alimemazine tartrate (Vallergan) has been moved from the list of exclusion medication (5.2.2) to be included in the medication that requires a 14-day washout (5.2.4). In addition, the text relating to exclusion drugs has been amended. This reflects the decision that children who have been taking exclusion drugs for less than 2 months must be excluded, however those children who have been taking exclusion drugs for more than 2 months can still be included in the trial as it is considered that they will have adjusted to their medication after 2 months.
31	The drug alimemazine tartrate (Vallergan) has been moved from the list of exclusion. In addition, the text relating to exclusion drugs has been amended, reflecting the decision that children who have been taking exclusion drugs for more than 2 months can still be included in the trial as it is considered that they will have adjusted to their medication after 2 months.
77	References updated as appropriate to include supporting documents for age reduction.

Fifth substantial amendment Version 5.0 09/07/2008 to Version 6.1 04/03/2009 (Version 6.0 27/01/2009 was submitted to the MREC and required additional amendments prior to approval)

Page No.	Comment
Throughout	Updated version and date; updated cross-referencing to sub-sections and references
10-11	Amendment to the number of participating sites in the trial summary. Amendment of figure 1 to remove the reference to the completion of the neuropsychological electronic tests (DENEM and MARS) at T0 and T+12. Amendment to figure 1 to remove the reference to actigraphy data collection at T+1 to T+4.
18	Removal of secondary outcomes: attention and vigilance assessed in care-givers using the car game from the DENEM project and attention and vigilance assessed in children using the Go/No go game from the MARS battery.
22-23	Table 1: Addition of pharmacy contact details for new centres.
37-38	Removal of reference to completion of neuropsychological electronic tests at T0 and T+12 and reference to actigraphy data collection at T+1 to T+4.
39	Table of schedule of study procedures: removal of neuropsychological electronic tests (DENEM and MARS) and removal of actigraphy data collection from weeks T+1 to T+4.
40-41	Amendment of text to reflect the removal of actigraphy data collection from T+1 to T+4.
41-42	Reduction in the number of Treatment Emergent Signs and Symptoms (TESS) specifically enquired about at each visit. If one of the removed TESS is reported spontaneously by a child or their care-giver they will still be reported as expected (based on their presence in the

	investigator's brochure and reviewed for relationship to study drug, severity and seriousness.
44-45	Removal of obsolete text and instructions relating to the completion of the neuropsychological electronic tests.
48	Removal of obsolete secondary outcomes: attention and vigilance assessed in care-givers using the car game from the DENEM project and attention and vigilance assessed in children using the Go/No go game from the MARS battery.
51	Table 4: Planned recruitment targets at each centre amended to reflect the addition of new centres and revised targets for existing centres based on performance to date.
55	Reduction in the number of TESS specifically enquired about at each visit.
74	Updated amendment summary.
84-87	Appendix A: Addition of contact details for the Principal Investigators at new centres and change to contact telephone number for Dr Tom Allport (Bristol Principal Investigator).
88-116	Patient information sheets and consent forms amended to remove the reference to completion of the neurophsychological electronic tests at T0 and T+12 and to remove the reference to the collection of actigraphy data from T+1 to T+4. The list of TESS recorded in the patient information sheets was reduced to reflect the above change to the protocol.

Fourth substantial amendment Version 4.0 06/05/2008 to Version 5.0 09/07/2008

Page No.	Comment
Throughout	Updated version and date
21-22	Table 1. Addition of pharmacy contact details for additional sites in Exeter and Torbay. Change of site name from St George's Hospital to Queen Mary's Hospital and change to fax number for pharmacy department.
49	Table 4. Change of St George's Hospital as a collaborating and recruiting centre to Queen Mary's Hospital. Addition of Royal Devon and Exeter Hospital and Torbay Hospital as collaborating and recruiting centres and reduction of Bristol's recruitment target from 19 to 10 patients.
81-82	Appendix A. Addition of Royal Devon and Exeter Hospital and Torbay Hospital as participating sites.

Third substantial amendment Version 3.0 25/01/2008 to Version 4.0 06/05/2008

Page No.	**Comment**
Throughout	Updated version and date
21	Table 1. Updated pharmacy contact details for Nottingham and deletion of Nicola Cuff as one of the pharmacy contacts for Bristol as Nicola has left this post.
48	Addition of Gulson Hospital as a collaborating and recruiting centre and addition of Bristol Royal Hospital for Children as a recruiting centre.
79-80	Addition of two health centres in Bristol and Gulson Hospital in Coventry as participating sites and change to Professor Turk's contact details.

Second substantial amendment Version 2.3 03/12/07 to Version 3.0 25/01/08

Page No.	**Comment**

Throughout	Updated version and date
18	Addition to exclusion criteria of current use of sedative or hypnotic drugs, including Chloral hydrate and Triclofos.
30	Addition of sedative and hypnotic drugs as prohibited medications throughout the trial.
33	Clarification that the sleep hygiene period should be a minimum of four weeks duration, but that it can be extended to a maximum of six weeks if required, to allow flexibility in the scheduling of the randomisation visit.
60-61	Clarification that if children are unable to provide assent, this should be documented in the medical notes and recorded on the age and stage of development specific PISC.
64	Clarification that dates of conducting the assent (as well as the consent) process should be recorded in the medical notes.

85 Addition to the parent PISC, of sedative and hypnotic drugs as prohibited medications for the duration of the trial.

Non-substantial amendments Version 2.2 31/10/07 to Version 2.3 03/12/07

Page No.	**Comment**
Throughout	Updated version and date; correction of typographical and grammatical errors; updated cross-referencing to sub-sections.
4	Change to MCRN CTU fax number and change to trial statistician's telephone number.
25	At T+4W, 7, rather than 8 weeks' supply of the current dose of IMP should be issued.
28	Clarification that unblinding can be performed if it is essential to treat serious, rather than severe (as previously stated) adverse events.
29	Clarification that pharmacy will dispense blister packs into blank cartons, and that local dispensing labels will be put onto the blank cartons, rather than the blister packs themselves.
36	Deleted reference to the provision of equipment for salivary sampling at T+4W visit.
39	Clarification that RPs may visually compare the actigraphy output with the sleep diaries either on return to the office, or at the home visits. If carried out at the office the RPs will telephone the family if required to resolve any discrepancies.
39	Clarification that 'final wake up time', rather than 'get up time' is recorded by parents in the sleep diary.
40	Section 8.4.2 incorrectly stated that seizure diaries are reviewed at the T+11W phone call. A home visit, not a phone call is carried out at T+11W.
43	Children with a developmental age of less than 5 years are unlikely to be able to complete the go/no go task. Rather than using the ABAS questionnaire to obtain an estimate of developmental age, the parents will be asked whether they think their child's overall level of functioning is equal to or greater than that of the average 5 year old.
43	Changed from long to medium track length for car game and changed the term 'excellent' driver to 'racing' driver.
59-60	Clarification that consent for registration (T-4W clinic visit) can be obtained by any qualified member of the research team, to whom this task has been assigned on the signature and delegation log.
60-61	Section 11.3 amended to reflect that the original of the consent/assent forms will be filed in the child's medical notes and one copy will be filed in the investigator site file, one copy will be sent to the MCRN

	CTU and one copy will be given to the child's parent/legal representative.
63	Clarification of what constitutes source data/documents for the trial.
66	Clarification of requirements for document retention at participating sites.
69	Section 16.2 amended to refer to the Data Monitoring Committee as DMC, rather than IDSMC.
80-91	Parent information sheet and consent form: correction of typographical errors; clarification that the time the child finally woke up (rather than got up) in the morning is recorded on the sleep diary. Deletion of reference to completion of computerised tasks at screening and collection of saliva samples on the evening prior to the T0 clinic visit and clarification that the quality of life questionnaires are only carried out at two time points during the study. These amendments were approved in the protocol text as part of the first substantial amendment; however the text within the patient information sheet was not updated at this time. The cross representing saliva sampling has been moved from the first home visit (T-2W) to the second clinic visit (T0W) in the table within the information sheet.
92-94	Parent genetic sub-study information sheet and consent form: correction of typographical errors.
95-102	Young persons' information sheet and consent form: correction of typographical errors, deletion of reference to completion of computerised tasks at screening, and insertion of reference to computerised tasks at the second clinic visit. Information has been added regarding opening the capsules if the child is unable to swallow them. Amendment of the assent form to state that the 'researcher' (rather than doctor) who explained the project needs to sign the form. Addition of instructions for copying and filing information sheets and consent forms.
103-108	Children's information sheet and consent form: correction of typographical errors, deletion of reference to completion of computerised tasks at screening, and insertion of reference to computerised tasks at the second clinic visit. Amendment of the assent form to state that the 'researcher' (rather than doctor) who explained the project needs to sign the form and addition of instructions for copying and filing information sheets and assent forms.
109-112	Young persons' genetic sub-study information sheet and consent form: amendment of the assent form to state that the 'researcher' (rather than doctor) who explained the project needs to sign the form and addition of instructions for copying and filing information sheets and assent forms.
124	Change to accountability log: 49 (rather than 56) capsules of the current dose should be dispensed at T+4W.

Non-substantial amendments Version 2.1 20/09/07 to Version 2.2 31/10/07

Page No.	**Comment**
81	Parent information sheet amended to reflect the change in the procedure for saliva sample collection that was approved as part of the first substantial amendment.

Non-substantial amendments Version 2.0 17/08/07 to Version 2.1 20/09/07

Page No.	**Comment**

21	Table 1. Correction of name and email address from Nicola Cuss to Nicola Cuff and nicola.cuss@nbt.nhs.uk to nicola.cuff@nbt.nhs.uk. Correction of telephone number for University College London Pharmacy from 0845 155 000 to 0845 1555 000.
37	Cross added to Table 2, Schedule of Study Procedures, to indicate completion of Epworth Sleepiness Scale at study completion (T+12W)
53-54	Change of causality opinion option for the reporting PI from 'definitely related' to 'almost certainly related'.
53	Change of outcome criteria for SAEs and SUSARs from 'ongoing at death' to 'ongoing at final follow-up'.

First substantial amendment Version 1.0 26/04/07 to Version 2.0 17/08/07

Page No.	**Comment**
Throughout	Updated version and date; correction of typographical and grammatical errors; reference to 'ASD questionnaire' replaced with correct name of 'SCQ questionnaire; addition of email and tel no. when MCRN CTU referred to; updated cross-referencing to sub-sections and references
9	Updated list of abbrieviations
10-11	Clarification of text in trial summary
13	Clarification of patient pack allocation
17	Clarification of outcome measures, removal of Kidscreen-10 questionnaire and addition of evaluation form for sleep hygiene booklet and addition of Epworth Sleepiness Scale
18-19	Inclusion/exclusion revised to replace Vineland assessment with Adaptive Behaviour Assessment System (ABAS); criterion text reworded to provide easier reference; presence/absence of sleep apnoea no longer determined using Children's Sleep Habits Questionnaire due to limited validation of cut-offs; addition of compliance check with sleep diaries as an inclusion criteria at T0; addition of: use of beta blockers within 7 days, allergy to melatonin and regular alcohol consumption as exclusion criteria
20	Clarification of screening procedure and documentation
20	Replacement of Vineland with ABAS
20	Consent/assent forms from T-4W to be sent to MCRN CTU within 7 days of registration
21	Updated contact details for pharmacy contact. Replacement of Bristol Royal Hospital for Children with Southmead Hospital (see also page 48)
23	Label description amended to reflect replacement of HTA reference with EudraCT number. Process for ordering and delivery of trial supplies amended
24-25	Expanded details relating to storage and destruction of trial supplies
25-26	Clarified procedures for mixing capsule contents in a vehicle for administration
28	Clarification of unblinding process
29-30	Destruction details added
30	Trade name of alimemazine tartrate added
33	Clarification of procedure for dose increments
34-36	Replacement of Vineland with ABAS, clarification of questionnaires to be completed; addition of sleep habits booklet evaluation form and CSHQ at T0; volume of trial medication supplied updated and explained; timing of obtaining salivary samples amended

37	Table of schedule of study procedures: replacement of Vineland with ABAS, removal of kidscreen questionnaire, addition of sleep hygiene evaluation form and addition of Epworth Sleepiness Scale and addition of CSHQ at T0
38	Sleep diaries have been piloted and amended, therefore text updated to reflect amended diary
39	Schedule for downloading actigraph data clarified
39-40	Bulleted TESS criteria simplified 'Somnolence' and 'fatigue' defined
40-41	Revision of genetic sub-study section to clarify that the research will involve a genome-wide association study
43	Vineland changed to ABAS; addition of CSHQ at T0
44	Removal of Kidscreen assessment; addition of Epworth Sleepiness Scale; clarification of CSDI scoring
45	Clarification of time points for salivary sampling
46	Primary outcome statistical analysis amended to reflect changes to sleep and seizure diaries
47	Secondary outcome measures amended as per page 17 update of endpoints
48	Replacement of Bristol Royal Hospital for Children with Southmead Hospital; change in recruitment target at Evelina Children's Hospital and St Georges Hospital
49-50	Revision of genetic sub-study analysis section to reflect genome-wide association study
53	Rewording of outcomes for SAEs and SUSARs
54	Additional detail on procedures by which research practitioners report SARs, SAEs and SUSARs to MCRN CTU
59	Clarification that all substantial amendments will be submitted for review
62	Clarification that notification of substantial amendments will be submitted to MHRA
63	Amended details of how source data will be indicated in eCRFs
71	Amendment summary
73-75	Updated references
76-77	Change to PI for Derbyshire Children's Hospital; change to Bristol site details
78-110	Patient information sheets and consent forms amended to clarify when and how saliva samples to be collected; stage of consent (registration at T-4 and randomisation at T0) and table of procedures in parent patient information
112-114	Amended instructions for collection of salivary samples and addition of version control
119	Removed block sizes from shipment request and addition of version control
120-121	Addition of version control to nurse's script for providing sleep booklet
122-123	Amended drug accountability log and addition of version control
125-127	Additon of Instructions for collection of DNA samples

19 REFERENCES

(1) Arendt J, Skene D, Middleton B, Lockley SW, Deacon S. Efficacy of melatonin treatment in jet lag, shift work and blindness. Journal of biological rhythms 1997;12(6):604-17.

(2) Herxheimer A, Petrie KJ. Melatonin for the prevention and treatment of jet lag. Cochrane Database Syst Rev 2002;(2):CD001520.

(3) Jan JE, Espezel H, Appleton RE. The treatment of sleep disorders with melatonin. Dev Med Child Neurol 1994 Feb;36(2):97-107.

(4) Wiggs L. Sleep problems in children with developmental disorders. J R Soc Med 2001 Apr;94(4):177-9.

(5) Quine L. Sleep problems in children with mental handicap. J Ment Defic Res 1991 Aug;35 (Pt 4):269-90.

(6) Miyamoto A, Oki J, Takahashi S, Okuno A. Serum melatonin kinetics and long-term melatonin treatment for sleep disorders in Rett syndrome. Brain Dev 1999 Jan;21(1):59-62.

(7) Alvarez B, Dahlitz MJ, Vignau J, Parkes JD. The delayed sleep phase syndrome: clinical and investigative findings in 14 subjects. J Neurol Neurosurg Psychiatry 1992 Aug;55(8):665-70.

(8) Palm L, Blennow G, Wetterberg L. Correction of non-24-hour sleep/wake cycle by melatonin in a blind retarded boy. Ann Neurol 1991 Mar;29(3):336-9.

(9) Palm L, Blennow G, Wetterberg L. Long-term melatonin treatment in blind children and young adults with circadian sleep-wake disturbances. Dev Med Child Neurol 1997 May;39(5):319-25.

(10) Jan MJ. Melatonin for the treatment of handicapped children with severe sleep disorders. J Pediatric Neurology 2000;23(3):229-32.

(11) Hung J, Appleton RE, Nunn AJ, Rosenbloom L. The use of melatonin in the treatment of sleep disturbances in children with neurological and behavioural disorders. Journal Pediatr Pharm Pract 1998;3:250-6.

(12) McArthur AJ, Budden SS. Sleep dysfunction in Rett syndrome: a trial of exogenous melatonin treatment. Dev Med Child Neurol 1998 Mar;40(3):186-92.

(13) O'Callaghan FJ, Clarke AA, Hancock E, Hunt A, Osborne JP. Use of melatonin to treat sleep disorders in tuberous sclerosis. Dev Med Child Neurol 1999 Feb;41(2):123-6.

(14) Ayyash HF, Morton R, Alfanek H, Preece P. Melatonin for the treatment of children with sleep disorders. Arch Dis Child 2005;90 (suppl II):A27-A28.

(15) Puri S, Broderick J, Parmar V, Tizzard E. Longterm use of melatonin to treat sleeping disorders in children with complex developmental disorders. Arch Dis Child 2005;90 (suppl II):A28.

(16) Phillips L, Appleton RE. Systematic review of melatonin treatment in children with neurodevelopmental disabilities and sleep impairment. Dev Med Child Neurol 2004 Nov;46(11):771-5.

(17) Dodge NN, Wilson GA. Melatonin for treatment of sleep disorders in children with developmental disabilities. J Child Neurol 2001 Aug;16(8):581-4.

(18) Smits MG, Nagtegaal EE, van der HJ, Coenen AM, Kerkhof GA. Melatonin for chronic sleep onset insomnia in children: a randomized placebo-controlled trial. J Child Neurol 2001 Feb;16(2):86-92.

(19) Smits MG, van Stel HF, van der HK, Meijer AM, Coenen AM, Kerkhof GA. Melatonin improves health status and sleep in children with idiopathic chronic sleep-onset insomnia: a randomized placebo-controlled trial. J Am Acad Child Adolesc Psychiatry 2003 Nov;42(11):1286-93.

(20) Coppola G, Iervolino G, Mastrosimone M, La TG, Ruiu F, Pascotto A. Melatonin in wake-sleep disorders in children, adolescents and young adults with mental retardation with or without epilepsy: a double-blind, cross-over, placebo-controlled trial. Brain Dev 2004 Sep;26(6):373-6.

(21) Gupta M, Aneja S, Kohli K. Add-on melatonin improves sleep behavior in children with epilepsy: randomized, double-blind, placebo-controlled trial. J Child Neurol 2005 Feb;20(2):112-5.

(22) Buscemi N, Vandermeer B, Hooton N, Pandya R, Tjosvold L, Hartling L, et al. The efficacy and safety of exogenous melatonin for primary sleep disorders. A meta-analysis. J Gen Intern Med 2005 Dec;20(12):1151-8.

(23) Wassmer E, Ross C, Whitehouse W. Therapeutic options for melatonin use in children. Paed Perinat Drug Therapy 2000;4:14-20.

(24) Cavallo A, Good WV, Douglas RM, Succop P. Dose response to melatonin treatment for disordered sleep rhythm in a blind child. Sleep Med 2002 Mar;3(2):159-61.

(25) Jan JE, O'Donnell ME. Use of melatonin in the treatment of paediatric sleep disorders. J Pineal Res 1996 Nov;21(4):193-9.

(26) Defrance R, Quera-Salva MA. Therapeutic applications of melatonin and related compounds. Horm Res 1998;49(3-4):142-6.

(27) Zemlan FP, Mulchahey JJ, Scharf MB, Mayleben DW, Rosenberg R, Lankford A. The efficacy and safety of the melatonin agonist beta-methyl-6-chloromelatonin in primary insomnia: a randomized, placebo-controlled, crossover clinical trial. J Clin Psychiatry 2005 Mar;66(3):384-90.

(28) Sheldon SH. Pro-convulsant effects of oral melatonin in neurologically disabled children. Lancet 1998 Apr 25;351(9111):1254.

(29) Buscemi N, Vandermeer B, Hooton N, Pandya R, Tjosvold L, Hartling L, et al. Efficacy and safety of exogenous melatonin for secondary sleep disorders and sleep disorders accompanying sleep restriction: meta-analysis. BMJ 2006 Feb 18;332(7538):385-93.

(30) Waldron DL, Bramble D, Gringras P. Melatonin: prescribing practices and adverse events. Arch Dis Child 2005 Nov;90(11):1206-7.

(31) Salti R, Galluzzi F, Bindi G, Perfetto F, Tarquini R, Halberg F, et al. Nocturnal Melatonin Patterns in Children. J Clin Endocrinol Metab 2000 Jun 1;85(6):2137-44.

(32) Sutherland ER, Ellison MC, Kraft M, Martin RJ. Elevated serum melatonin is associated with the nocturnal worsening of asthma. J Allergy Clin Immunol 2003 Sep;112(3):513-7.

(33) Campos FL, da Silva-Junior FP, de B, V, de Bruin PF. Melatonin improves sleep in asthma: a randomized, double-blind, placebo-controlled study. Am J Respir Crit Care Med 2004 Nov 1;170(9):947-51.

(34) Forsling ML, Wheeler MJ, Williams AJ. The effect of melatonin administration on pituitary hormone secretion in man. Clin Endocrinol (Oxf) 1999 Nov;51(5):637-42.

(35) Gupta M, Aneja S, Kohli K. Add-on melatonin improves quality of life in epileptic children on valproate monotherapy: a randomized, double-blind, placebo-controlled trial. Epilepsy Behav 2004 Jun;5(3):316-21.

(36) ncoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP. The role of actigraphy in the study of sleep and circadian rhythms. Sleep 2003 May 1;26(3):342-92.

(37) Melke J, Brotos GH, Chastel P, Betancur C, Nygren G, Anckarsater H, et al. Abnormal Melatonin Synthesis in Autism and Hyperactivity. Molecular Physchiatry 2007.

(38) Begg C, Cho M, Eastwood S, Horton R, Moher D, Olkin I, et al. [Improving the quality of reports on randomized controlled trials. Recommendations of the CONSORT Study Group]. Rev Esp Salud Publica 1998 Jan;72(1):5-11.

(39) Moher D, Schulz KF, Altman D. The CONSORT Statement: revised recommendations for improving the quality of reports of parallel-group randomized trials 2001. Explore (NY) 2005 Jan;1(1):40-5.

(40) Wiggs L, Stores G. A randomised controlled trial of behavioural intervention for sleepiness in children with autism. In Preparation 2007.

(41) Quine L, Pahl J. Examining the causes of stress in famalies with severely mentally handicapped children. British Journal of Social Work 1985;15:501-17.

(42) Reich DE, Goldstein DB. Detecting association in a case-control study while correcting for population stratification. Genet Epidemiol 2001 Jan;20(1):4-16.

(43) The CONSORT Group. CONSORT Statement. CONSORT 2007 [cited 2007 Jan 29];Available from: URL: http://www.consort-statement.org/

20 APPENDICES

Appendix A: Participating Sites

Northern Centres:

Lead Site:	Dr Richard Appleton (Chief Investigator) Consultant Paediatric Neurologist The Roald Dahl EEG Unit Alder Hey Hospital Eaton Road, Liverpool, L12 2AP Tel: 0151 252 5851 Fax: 0151 252 5152 E-mail: Richard.Appleton@alderhey.nhs.uk
Participating Site:	Dr Timothy Martland (Principal Investigator) Consultant Paediatric Neurologist Dept of Neurology Royal Manchester Children's Hospital Oxford Road, Manchester, M13 9WL Tel: 0161 701 2346 Fax: 0161 701 2555 Email: Timothy.Martland@CMMC.nhs.uk
Participating Site:	Dr Evangeline Wassmer (Principal Investigator) Consultant Paediatric Neurologist Neurology Department Birmingham Children's Hospital Steelhouse Lane, Birmingham, B4 6NH Tel: 0121 333 8152 Fax: 0121 333 8151 Email: evangeline.wassmer@bch.nhs.uk or bch.wassmer@yahoo.co.uk
Participating Site:	Dr Evangeline Wassmer (Principal Investigator) Consultant Paediatric Neurologist Gulson Hospital Gulson Road, Coventry CV1 2HR Tel: 0121 333 8152 Fax: 0121 333 8151 Email: evangeline.wassmer@bch.nhs.uk or bch.wassmer@yahoo.co.uk
Participating Site:	Prof Imti Choonara (Principal Investigator) Professor in Child Health Academic Division of Child Health (University of Nottingham), The Medical School Derbyshire Children's Hospital Uttoxeter Road, Derby, DE22 3DT Tel: 01332 724 693 Fax: 01332 724 697 Email: Imti.Choonara@nottingham.ac.uk
Participating Site:	Dr Phillip Preece (Principal Investigator) Consultant Paediatrician Chesterfield Royal Hospital Calow, Chesterfield, S44 5BL Tel: 01246 512 520 Fax: 01246 512 620 Email: Philip.preece@chesterfieldroyal.nhs.uk
Participating Site:	Dr William Whitehouse (Principal Investigator) Senior Lecturer in Paediatric Neurology School of Human Development, Academic Division of Child Health, Queen's Medical Centre, Derby Road Nottingham, NG7 2UH Tel: 0115 924 9924 ext 44476 Fax: 0115 970 9382 Email: william.whitehouse@nottingham.ac.uk

Participating Site:	Dr Megan Thomas (Principal Investigator) Consultant Community Paediatrician Blenheim House Child Development and Family Support Centre 145-147 Newton Drive Blackpool, FY3 8LZ Tel: 01253 651 615 Fax 01253 397 008 Email: dr.thomas@bfwhospitals.nhs.uk
Participating Site:	Dr Jayaprakash A Gosalakkal (Principal Investigator) Consultant Paediatric Neurologist Leicester Royal Infirmary Infirmary Square LE15WW, Leicester Tel: 01162 585 564 Fax: 01162 587 637 Email: Jayprakash.gosalakkal@Uhl-tr.nhs.uk
Participating Site:	Dr Valerie Harpin (Principal Investigator) Consultant Paediatrician (Neurodisability) Child Development and Neurodisability Ryegate Children's Centre Sheffield Children's NHS Foundation Trust Tapton Crescent Road Sheffield S10 5DD Tel 01142 717609 FAX 01142 678296 Email: Val.Harpin@sch.nhs.uk
Participating Site:	Dr Adrian Hughes (Principal Investigator) Neonatal Unit, Arrowe Park Hospital, Upton, Wirral, CH49 5PE Tel: 0151 604 7071 Fax: 0151 604 7096 Email: adrian.hughes@whnt.nhs.uk

Southern Centres:

Lead Site:	Dr Paul Gringras (Chief Investigator) Consultant in Paediatric Neurodisability Evelina Childrens Hospital St Thomas' Hospital Lambeth palace Road, London, SE1 7EH Tel: 0207 188 7188 ext 84649 Fax: 0207 188 4629 E-mail: paul.gringras@gstt.nhs.uk
Participating Site:	Dr Alastair Sutcliffe (Principal Investigator) Senior Lecturer in Child Health (Honorary Consultant) University College London Institute of Child Health 1st Floor West 250 Euston Road, London, NW1 2PQ Tel: 0207 380 9676 Fax 0207 389 9789 E-mail: a.sutcliffe@medsch.ucl.ac.uk
Participating Site:	Dr Tom Allport (Principal Investigator) Honorary Senior Clinical Lecturer Community Child Health/Neurodisability Centre for Child and Adolescent Health Hampton House, Bristol, BS6 6JS Tel 0117 340 8089 Fax 0117 331 0891 E-mail: allportt@gn.apc.org
Participating Site:	Dr Tom Allport (Principal Investigator) Honorary Senior Clinical Lecturer Southmead Hospital Westbury-On-Trym, Bristol,BS10 5NB Tel: 0117 340 8089 Fax: 0117 331 0891 E-mail: allportt@gn.apc.org
Participating Site:	Dr Tom Allport (Principal Investigator) Honorary Senior Clinical Lecturer Montpelier Health Centre (Clinic Site) Bath Buildings, Bristol, BS6 5PT
Participating Site:	Dr Tom Allport (Principal Investigator) Honorary Senior Clinical Lecturer Charlotte Keele Health Centre (Clinic Site) Seymour Road, Easton Bristol BS5 OUA
Participating Site:	Dr Ron Smith (Principal Investigator) Consultant Paediatrician Department of Child Health Royal Devon and Exeter Foundation NHS Trust Barrack Road Wonford, Exeter, EX2 5DW Tel: 01392 406145 Fax: 01392 403128 Email: Ron.Smith@rdeft.nhs.uk
Participating Site:	Dr Clive Sainsbury Consultant Paediatrician Torbay Hospital, Lawes Bridge Torquay, TQ2 7AA Tel: 01392 654824 Fax: 01803 617174 Email: Clive.Sainsbury@nhs.net
Participating Site:	Dr Zenobia Ziawalla (Principal Investigator) Consultant in Paediatric Neurophysiology West Wing, John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU Tel: 01865 226315 Fax: 01865 763461 Email: Zenobia.Zaiwalla@obmh.nhs.uk

Participating Site:	Professor Jeremy Turk (Principal Investigator) Honorary Consultant Child & Adolescent Psychiatrist Sandalwood Unit, Queen Mary's Hospital, Roehampton Lane, Roehampton, London, SW15 5PN Tel: 0208 487 6049 Fax: 0208 785 0693 Email: jturk@sgul.ac.uk
Participating Site:	Dr Catherine Hill (Principal Investigator) Senior Lecturer Child Health Paediatric Neuroscience Mail point 803 G G Level Centre Block Southampton General Hospital Southampton, SO16 6YD Tel: 02380 796091 (University) Tel: 02380 716633 (NHS) Fax: 02380796420 Email: C.M.Hill@soton.ac.uk
Participating Site:	Dr Johann te Water Naude (Principal Investigator) Consultant Paediatric Neurologist, Paediatric Neurology Children's Centre Department of Child Health University Hospital of Wales Heath Park,Cardiff,CF14 4XW Tel: 029 2074 3540 Fax: 029-2074-4898 Email: tewaternaudeja@Cardiff.ac.uk

Appendix B: Patient Information and Consent Forms

(To be presented on local headed paper and include MENDS logo)

Centre Name and Number: xxx

Parent Information and Consent Form: Version 3.0 Date 27/01/09

MENDS: The use of MElatonin in children with Neuro-developmental Disorders and impaired Sleep; a randomised, double-blind, placebo-controlled, parallel study

ISRCTN05534585

Parent/Guardian Information Sheet and Consent Form

Where the word "parent" is used, please read parent/guardian i.e. those who have parental responsibility, which may include a legal representative e.g. grandparent.

Parents and children are being invited to take part in this research study. Before you decide about this it is important for you to understand why the research is being done and what it will mean for you and your child. Please take time to read the following information carefully. Talk to others about the study if you wish.

- Part 1 tells you the purpose of the study and what will happen if you take part.
- Part 2 gives you more detailed information about how the study will be organised.

Please ask us if there is anything that is not clear or if you would like more information.

Part 1.

What is the purpose of the study?

Melatonin is a natural substance found in the body and produced by a gland in our brain called the pineal gland. The job of melatonin is to control the times that we fall asleep and wake up. Usually more melatonin is produced and released into our bodies in the evening.

Children with neurological and/or developmental disorders often have problems with their sleep pattern. Other research studies in adults have shown that melatonin is helpful in treating sleep problems. There are very few research studies which have suggested that melatonin may be of benefit in children with developmental delay.

Melatonin is not licensed in the UK but is used regularly to treat children with sleep problems. Some studies suggest it helps children to fall asleep and to have longer periods of continuous sleep but we do not know for sure if it works. The only way to find out for certain if it works is to compare children who are given melatonin with those who do not receive any melatonin in a research study. This sort of study is called a randomised controlled trial or RCT.

Why has my child been chosen?

Your child has been asked to take part in this study because they have been diagnosed with a neurological and/or developmental disorder and they have some problems sleeping. Your community paediatrician has referred you to (or is going to refer you to) a specialist clinic, where this study is being carried out. We will be recruiting approximately 200 children from 12 centres in England.

Does my child have to take part?

No, taking part is completely voluntary. It is up to you and your child (if they can) to decide whether or not to take part, or to drop out at any time, without giving a reason. A decision to leave the study, or a decision not to take part, will not change the standard of care you and your child receive now or in the future. If you do take part, you will be given this information sheet to keep and be asked to sign a consent form. The study doctor may also stop your child from taking part in the trial at any time if they feels it is necessary.

Your study doctor and/or nurse may ask your permission to make an audio recording of the interview when they are inviting you to take part in the MENDS trial. This is because another study, called RECRUIT, is being carried out to find out what it is like for parents when their child is invited to take part in a clinical trial. With your permission, your study doctor will also pass your contact details to the researchers carrying out the RECRUIT study, who will make direct contact with you at a later date.

You do not have to agree to the interview being recorded, and recordings will only be given to RECRUIT researchers if you consent to take part in that study, otherwise it will be deleted.

What will happen to my child if we agree to take part and how long will it take?

The total study period is 16 weeks.

Screening

If you are happy to take part, and are satisfied with the explanations from your research team, you will be asked to sign a consent form at the first clinic visit. If your child is able to understand the research and is happy to take part and can write their name, they will be asked to sign an “assent” form with you, if they want to. You will be given a copy of the signed information sheet and consent/assent forms to keep. Once consent has been taken your child will be registered for the study and you will be asked some questions to make sure that they are able to take part. You and your child will also be asked to complete two questionnaires about sleep habits, which will take approximately 15 minutes to complete. The study doctor will ask some questions about your child’s medical history and will physically examine your child to make sure they can take part in the study.

Four week Behavioural Intervention

At the first clinic visit you will be provided with an information booklet which gives you some ideas about techniques that you can use to help your child to sleep better. These techniques have been shown to reduce sleeping problems of children with developmental disorders. You will be asked to use these methods (and no other

treatments or methods) for the next four weeks. Whilst trying these methods we would like you to complete a sleep record (diary) so that for each day and night we can see the time they went to bed, the time they fell asleep, any awakenings during the night and the time they finally woke up in the morning. If your child has epilepsy we would also like you to keep a diary recording how often they have seizures and what type of seizures they have.

For these four weeks we would also like your child to wear what looks like a wristwatch but is actually a special piece of equipment called an actiwatch or actigraph which is used to measure movement.

The actigraph records movement for 4 weeks and we copy the results of these movements onto our computers. We can then use the information along with your sleep diary to measure when your child was asleep or awake.

In the middle of this four week period (two weeks after your clinic visit and study registration) the research nurse will visit you at home to look at any changes in your child's sleep patterns as a result of using the techniques described in the booklet. If you and your child agree to the genetic testing (see additional information sheet) you will be asked to complete another consent/assent form and a sample of saliva will be taken at this visit.

At the end of this four week period, on the evening before your second clinic visit we would like you to obtain some saliva from your child if your child is able to do this. This will allow us to measure your child's normal levels of melatonin before they start treatment. We would like you to collect saliva every hour from 5pm up until your childs bedtime. To obtain a saliva sample you will need to ask your child to spit into a small container. If your child can not spit into the container then you can wipe one or two small sponges on sticks around your child's mouth to soak up their spit. (Further instructions will be provided separately).

Treatment Allocation

If your child continues to meet the study criteria at the end of this four week period and still has sleep problems they will be asked to enter into the study.

MENDS is a randomised controlled trial (RCT) in which we will be comparing children who receive melatonin with those who do not. We need to be sure that we are being fair when judging the effect of melatonin and we do this by having two treatment groups – both groups will be given capsules that are disguised to look exactly the same but only one of the groups will actually receive capsules containing the active medicine. The other group will be given capsules that are a "dummy treatment", or placebo, and don't contain any melatonin.

To confirm that you are happy for your child to continue with the study and be given the study treatment, you will be asked to sign another consent form. If your child is able to they will be asked to sign an "assent" form.

Half of the children in the study will be given melatonin capsules and the other half will be given placebo capsules, so your child's chance of getting melatonin is one in two. In order to make accurate comparisons we need to be sure that both groups have similar children in them and we do this by using a special computer program. This means that whether your child receives the test medicine or placebo will be

decided at random or by chance. You and your child will not be able to choose which one you get.

This trial is “double blind” so neither you (nor your child), your child’s doctor, research nurses, or pharmacist will know which of the treatment groups your child has been put into (although, if your doctor needs to find out he/she can do so). This is so we can be sure the information provided about both treatment groups is balanced, or unbiased, and not swayed by knowledge of whether it is the test medicine or the placebo that is being given. These measures help us to make a fair judgement about the effect of melatonin when the results between the two groups (melatonin and placebo) are compared at the end of the study.

After consent (and assent if appropriate) has been taken, you will be asked to complete some questionnaires on sleep habits, behaviour and quality of life.

Twelve week treatment period

Your child will be checked regularly by the research team for 12 weeks after they start taking their study treatment. These checks will be by the research nurses visiting you or telephoning you at home or by you and your child attending the out patient clinic. During this period you will be regularly asked about your child’s health and their sleep habits. For the eleventh week of this period your child will be required to wear the actiwatch or actigraph. We would like you to continue to complete the sleep diary and seizure diary (if your child also has epilepsy) throughout the twelve-week follow-up period and during week 10 we would like you to collect another set of saliva samples if your child can do this.

We have drawn a table on the next page to show what will happen at each of the checks or during telephone calls. The left hand column shows the study procedures and the top row is the time in weeks. An X is used in the boxes to mark when a procedure will be carried out.

Week 12

Week 12 is when the study finishes for your child. At the end of this week you and your child will return to clinic where you will both repeat the questionnaires and computer tests that you did before treatment started. The study doctor will also physically examine your child during this visit.

Table of study procedures

	4 weeks using booklet			12 week treatment period						
Time frame (weeks)	**0**	**2**	**4**	**1-3**	**4**	**5-6**	**7-9**	**10**	**11**	**12**
Procedures	**Clinic visit**	**Home visit**	**Clinic visit**	**Home visits**	**Home visit**	**Tel. call**	**Tel. call**	**Tel. call**	**Home visit**	**Clinic visit**
Sign consent form	X	X	X							
Eligibility questions and assessments	X		X							
Sleep behaviour intervention (booklet)	X	X								
Sleep habits questionnaires	X		X							X
Quality of life and behaviour questionnaires			X							X
Complete sleep (and seizure) diary	X	X	X	X	X	X	X	X	X	
Actigraph worn	X	X	X						X	
Treatment given			X	X	X	X	X	X	X	
Dose increase possible				X	X	X				
Full physical exam	X		X							X
Assessment of side effects				X	X	X	X	X	X	X
Salivary samples			X					X		
Genetics sample		X								

What does my child have to do if we agree to take part?

If you and your child do decide to take part in the trial it is important that you and your child follow the instructions and advice given to you by the study doctor and research nurse. If you are unsure about anything, please ask. Before taking part and throughout the study it is important that you tell the study doctor (or any of the staff) about any changes in your child's health that you may have noticed since you last saw them and tell them about any other medication they are taking. You will need to return all the medication packaging and unused medication to your research nurse at each home or clinic visit. It is important to make sure that any other doctor your child visits knows they are taking part in this study. You will be provided with a card with details of contact names and telephone numbers for the study. The doctor at the sleep clinic will write to your GP to let him/her know that you are taking part in the research study.

If the results of the second clinic visit mean that your child is suitable to take part in the study, she/he will start taking study medication within 48 hours of this visit. You will need to give your child one capsule 45 minutes before bedtime, every day for the next twelve weeks of the study. If your child has problems tolerating the medication your study doctor may ask you to stop the medication. It is very important that you make sure that the medication is stored safely and kept out of the reach of children.

During the sixteen week study period we would like you to complete a sleep diary of your child's sleeping habits. If your child has epilepsy we will also ask you to complete a seizure diary describing the number and type of seizures they have. At three time points during the sixteen week study period we will ask you to complete some questionnaires about your child's sleep habits. At two points in the study we will ask you about your family's quality of life

What is the drug, device or procedure that is being tested?

Melatonin is a natural substance responsible for everyone's sleep–wake cycle. The melatonin your child might receive (if they are randomised to the active treatment) has been made specifically for this study. One out of every two children taking part in the study will receive melatonin and one out of every two children will receive the placebo (a dummy drug which looks identical to the test medicine).

The melatonin or placebo will be given orally within a gelatine capsule. If your child is not able to swallow a capsule or has a nasogastric or gastrostomy feeding tube, the capsule can be opened and the contents mixed with orange juice, strawberry yogurt, strawberry jam, semi skimmed milk or water.

All children will start on a 0.5mg per day dose of either the melatonin or placebo. At the end of the first week of treatment this dose will be reviewed. If there has been an improvement in your child's sleep habits they will remain on a dose of 0.5mg per day for the next week. However, if your child still has problems sleeping and meets a number of other criteria the dose will be increased to 2.0mg per day for the next week. If this dose does not improve your child's sleep problems further weekly increases are permitted to 6.0mg per day and then 12.0mg per day. Six weeks after randomisation no further dose increases are permitted and your child will remain on the dose given during this week for the remaining six weeks of treatment. If your child has any health problems during the treatment period that your doctor feels might be related to the medication they may reduce the medication dose or stop the medication.

The following medications (tablets or medicines) are not permitted during the study:

- melatonin (prescribed outside of the study)
- all beta blockers
- alcohol
- sedative and hypnotic medications including Chloral hydrate and Triclofos

Please inform your study doctor or nurse if your child is prescribed any new medications or if any changes are made to their current medications:

What are the alternatives for diagnosis or treatment?

There are limited available treatments for sleep problems in children with developmental disorders. The recommended treatment to try first is the use of the techniques described in the booklet you will be given as part of this study. Only if those are not successful would other alternative approaches be tried. These would most commonly either be melatonin or perhaps infrequent use of sedative or hypnotic medicines to help your child sleep. Sedative and hypnotic medicines are often not very helpful (either the effects they produce are small, or the effects wear off over time or for some children, they can show an unusual response and find themselves hyperactive and even less able to sleep).

What are the side effects of any treatment received when taking part?

The side effects that have been observed in other studies have been in small numbers of patients and have not been serious or long-term in nature.

Please look out for the presence of the following signs and symptoms in your child and report them to the study doctor or nurse when you next see or speak to them:

- sleepiness / drowsiness
- increased excitability
- seizures (newly developed or worsening/increase of existing seizures)
- coughing
- rashes
- abnormally low body temperature

We know that melatonin has a role in other body functions, not only sleep, so we can think about side-effects that might happen linked to these other roles. There isn't enough evidence from research to prove that melatonin causes these side-effects for certain. Knowing how melatonin works means that it could have an effect on growth and sexual development, it could make symptoms of asthma worse at night and it could also affect seizure control.

What are the other possible disadvantages and risks of taking part?

Melatonin treatment might harm the unborn child; therefore your child should not take part in this study if they are pregnant or breast-feeding. If your child is female and started menstruating we will ask whether she is sexually active. If she is we will ask her to consent to have a pregnancy test before taking part.

If your child does become pregnant during the course of the study, you and/or your child must tell your study doctor immediately so appropriate action can be discussed. Your child will be referred for specialist counselling on the possible risks to their unborn baby and arrangements will be offered to monitor the health of both your child and their unborn baby.

What are the possible benefits of taking part?

Few studies have looked at the effect of melatonin on sleeping problems, which is why we are doing this study. The studies that have been done have shown that melatonin may improve sleep for some people, including children with neurological and pyschological disorders. Benefits have included that children fall asleep quicker and have longer periods of continuous sleep during the night. The improvement in sleep habits has also been linked to improved behaviour during the day.

We cannot promise the study will personally help you or your child but the information we get might help improve the treatment of other children with neurodevelopmental disorders and sleep problems and their families.

What happens when the research study stops?

Once **all** children have completed the twelve weeks of study followup you will be told whether your child received melatonin or the placebo. This information will be provided in writing by your study doctor or nurse and a copy will be placed in your child's medical records.

It will be some time after your child has completed the study before it is known whether they were receiving active melatonin or placebo. When your child completes their participation his/her doctor will treat him/her according to normal clinical practice, which means that melatonin may continue to be prescribed but it is not likely to be exactly the same as the melatonin given in the study.

What if there is a problem?

Any complaint about the way you or your child have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

If you have any complaints about this research study, please contact the hospitals research and development department using the details below:

Will my child's taking part in the study be kept confidential?

Yes. All the information about your child's participation in this study will be kept confidential. The details are included in Part 2.

Contact Details:

You will always be able to contact a member of the research team to discuss your concerns and/or get help. Please call:

..... (Research Nurse)

..... (Principal Investigator)

This completes Part 1 of the Information Sheet.
If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.

Part 2

What if relevant new information becomes available?

Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your research doctor will tell you and your child about it and discuss whether you both want to or should continue in the study. If you or your child decide not to carry on, your research doctor will make arrangements for your child's care to continue. If you and your child decide to continue in the study you will be asked to sign an updated consent form and your child (where possible) will be asked to sign an updated assent form.

Also, on receiving new information your research doctor might consider it to be in your child's best interests to withdraw them from the study. He/she will explain the reasons and arrange for your child's care to continue.

If the study is stopped for any other reason, you will be told why and your child's continuing care will be arranged.

What will happen if my child or I don't want to carry on with the research?

If at any point you or your child decide to withdraw from the study, all unused medication will be collected for destruction. You or your child can withdraw from treatment, but continue to be followed up and have data collected as outlined in Figure 1 (actigraphy, sleep diaries, questionnaires). Alternatively you and your child can attend clinic as per their normal treatment and allow data from these visits to be used for the study.

Following withdrawal from the study your child will be treated according to local clinical practice. All data collected up until the time of withdrawal will be anonymised and included in the study analysis.

What if there is a problem?

Complaints:
If you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions (PI/RN Tel no.). If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure. Details can be obtained from the hospital.
Harm:
In the event that something does go wrong and your child is harmed during the research study there are no special compensation arrangements. If your child is harmed and this is due to someone's negligence then you may have grounds for a legal action for compensation against (name of NHS Trust) but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

Will my child's taking part in this study be kept confidential?

All information, which is collected, about you and your child during this study is considered confidential and giving this information to anyone else (called third parties) is not allowed with the exceptions noted below. The electronic and paper files used to record information in this study will be labelled with a unique trial registration and/or randomisation number. Medical information may be given to your child's doctor or other appropriate medical personnel responsible for their welfare.

In order to confirm that appropriate informed consent has been taken copies of you and your child's signed consent/assent forms will be sent to the Medicines for Children Research Network Clinical Trials Unit (MCRN CTU). The MCRN CTU is registered under the Data Protection Act 1998 and will ensure that you and your child's confidentiality are preserved.

If you and your child join the study, some parts of your child's medical records and the data collected for the study will be looked at by authorised persons from the Alder Hey Children's NHS Foundation Trust who are sponsoring the study. They may also be looked at by representatives of regulatory authorities and by authorised people from other NHS bodies to check that the study is being carried out correctly. Your child's medical records will be checked in the hospital and will not be removed from the hospital. All authorised individuals will have a duty of confidentiality to you and your child as research participants and nothing that could reveal your child's identity will be disclosed outside the research site. By signing the consent form you are giving permission for this to happen. In the event of the study results being sent to Health Authorities, or published, all your child's records will be kept confidential and your child's name will not be disclosed to anyone outside the hospital.

All documents and files relating to the study will be stored confidentially either at your local study site, at the MCRN CTU or both for up to a maximum of 15 years.

Involvement of the General Practitioner/Family doctor (GP)

With your consent, the study doctor will write to your child's GP to let them know that your child is taking part in the study. The study doctor may ask your child's GP for further medical information about them, if necessary.

What will happen to any samples my child gives?

As part of the main study saliva samples will be taken for the measurement of melatonin levels; this test would not normally be undertaken in clinical practice. If you and your child consent to the additional genetic testing a DNA sample will be obtained by collecting a sample of your child's saliva (see separate information sheet). These samples will be transferred to external laboratories and will be identified by special numbers to maintain your child's anonymity.

Will any genetic tests be done?

In addition to the main study we would also like to collect a genetic DNA sample from all children participating in the study. This is an optional extra, with a separate information sheet and consent form that will be provided at your first clinic visit. You and your child can still participate in the main study (outlined in this information sheet) without taking part in the additional genetic study.

What will happen to the results of the research study?

The results are likely to be published in the six months following the study. Your confidentiality will be ensured at all times and you will not be identified in any publication. At the end of the study, the results can be made available to you and/or your GP should you wish.

Who is organising and funding the research?

Alder Hey Children's NHS Foundation Trust is sponsoring this study; they have assigned the day to day running of the study to the Medicines for Children Research Network Clinical Trials Unit. If you take part it will be necessary for members of the Clinical Trials Unit and possibly regulatory authorities, to have access to your hospital medical records to check that the information from the study has been recorded accurately. Your medical records will be checked in the hospital and will not be removed from the hospital. By signing the consent form you are giving permission for this to happen. In the event of the study results being sent to Health Authorities, or published, all your records will be kept confidential and your name will not be given to anyone outside the hospital.

This study is funded by the Health Technology Assessment programme of the Department of Health. Funding for trial treatments is provided by Alliance Pharmaceuticals. Each collaborating site has been allocated funds for provision of general office supplies and to support pharmacy costs.

Who has reviewed the study?

The trial protocol has received the favourable opinion of both the North West Multi-centre Research Ethics Committee and the ..... Local Research Ethics Committee

THANK YOU FOR READING THIS INFORMATION SHEET.
WE HOPE YOU HAVE FOUND THIS SHEET HELPFUL.

(Form to be on headed paper)
Centre Number:

PARENT/GUARDIAN CONSENT FORM Version 3.0 Date 27/01/09

MENDS: The use of MElatonin in children with Neuro-developmental Disorders and impaired Sleep; a randomised, double-blind, placebo-controlled, parallel study

Name of Researcher:

	Please initial box
1. I confirm that I have read and understand the information sheet dated ……..…… (version ……....) for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason, and without my care/my child's care or legal rights being affected.	
3. I understand that relevant sections of any of my child's medical notes and data collected during the study may be looked at by responsible individuals from the Medicines for Children Research Network Clinical Trials Unit, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my child's records.	
4. I agree to my child's GP being informed of my child's participation in the study	
5. I agree to my contact details being disclosed to RECRUIT researchers*	
6. Please tick which statement applies a) I agree for my child to be ***registered for*** this study □ b) I agree for my child to be ***randomised into*** this study □	

* delete if not applicable for this centre

_____
Name of Patient

_____ _____ _____
Name of Parent Signature Date

_____ _____ _____
Researcher Signature Date

When completed, 1 for patient; 1 for researcher site file; 1 for MCRN CTU, 1 (original) to be kept in medical notes

(To be presented on local headed paper and include MENDS logo)

Centre Name and Number: xxx

MENDS: The use of MElatonin in children with Neuro-developmental Disorders and impaired Sleep; a randomised, double-blind, placebo-controlled, parallel study

ISRCTN05534585

Additional Parent/Guardian Information Sheet and Consent Form for Genetic sub-study: Version 1.2 Date 03/12/07

Where the word "parent" is used, please read parent/guardian i.e. those who have parental responsibility, which may include a legal representative e.g. grandparent.

What is the purpose of the study?

Genes are coded messages found in the cells of all living things that tell them how to develop. Children receive, or inherit, their genes from their parents and genetics is the study of how these coded messages control the features that are passed from parent to child. Some features are easy to see, such as hair and eye colour, but others are harder to detect, for example how our body responds to medicines.

Melatonin is a natural substance found in our body that controls the body clock. We know that the amount of melatonin released (or secreted) is controlled by our genes and that this is passed on from parent to child. No single gene has been found that controls melatonin secretion. We have some idea of which genes might be involved and they may also be involved in the development of autism and other learning disabilities. In this study we aim to:

- look at the relationships between sleep problems and melatonin levels.
- try to identify genes that are linked to the degree of sleep problems or melatonin level.
- try to identify genes that are linked to how melatonin is made in the body.
- try to identify genes that are linked to an individual's response to melatonin treatment.

Does my child have to take part?

No, taking part is entirely voluntary. If you and your child decide not to take part in this additional genetic study, you can still take part in the main study. A decision not to take part in this addtional study will not affect the standard of care you and your child receive now or in the future. If you do take part, you will be given this information sheet to keep and be asked to sign an additional consent form.

What will happen to my child if we agree to take part?

If you and your child agree to take part, the study nurse will need to collect a sample of your child's genes. This is done by collecting a saliva sample by wiping some small sponges on sticks around the inside of your child's mouth.

As the development of autism may be also be related to the same genes we are investigating for the release of melatonin, we would also like you to complete a short additional questionnaire called the 'Social communication questionnaire'.

What does my child have to do if we agree to take part?

Allow the study nurse to obtain a saliva sample.

What are the possible disadvantages and risks of taking part?

There are no risks associated with saliva collection.

What are the possible benefits of taking part?

This genetics study will not directly benefit your child. However, it will help us to understand the role of genes in sleep problems and melatonin levels. This might help us to know whether melatonin treatment will help a particular child before we give it to them.

Will my child's taking part in the study be kept confidential?

Yes. All the information about your child's participation in this study will be kept confidential. The details are included in Part 2 of the main information sheet.

What will happen to any samples my child gives?

The sample will be not be labelled with your child's name. It will be transferred to external laboratories where the genes can be investigated. Samples will be identified by special numbers so that we can link the sample to details collected in the main study but cannot otherwise identify your child. Results from individual children do not tell us very much information but we will collect samples from lots of children and hope that this research will inform future testing programmes, which would then be available later through the NHS.

(Form to be on headed paper)
Centre Name and Number: xxx

PARENT/GUARDIAN CONSENT FORM FOR GENETIC SUB-STUDY
Version 1.2 Date 03/12/07

MENDS: The use of MElatonin in children with Neuro-developmental Disorders and impaired Sleep; a randomised, double-blind, placebo-controlled, parallel study

Name of Researcher:

	Please initial box
1. I confirm that I have read and understand the information sheet dated ……..…. (version ……....) for the above study. I have had the opportunity to consider the information, ask questions and have these answered satisfactorily.	
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving a reason, and without my care/my child's care or legal rights being affected.	
3. I understand that relevant sections of any of my child's medical notes and data collected during the study may be looked at by responsible individuals from the Medicines for Children Research Network Clinical Trials Unit, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my child's records.	
4. I agree to my child's GP being informed of my child's participation in the study	
5. I agree to take part in the above study.	

_____
Name of Patient

_____ _____ _____
Name of Parent Signature Date

_____ _____ _____
Researcher Signature Date

When completed, 1 for patient; 1 for researcher site file; 1 for MCRN CTU, 1 (original) to be kept in medical notes

(To be presented on local headed paper and include MENDS logo)

Centre Name and Number: xxx

Young persons (11-15 years equivalent) Information and Consent Form
Version 2.0 Date 27/01/09

Part 1 – to give you first thoughts about the project

MENDS: The use of MElatonin in children with Neuro-developmental Disorders and impaired Sleep

We are inviting you to take part in some research. Before you decide if you want to join in it's important to understand why the research is being done and what it will mean for you. So please read this leaflet carefully. Talk about it with your family, friends, doctor or nurse if you want to.

Please ask us if there is anything that is not clear or if you would like more information. Thank you for reading this.

Why are we doing this research?

We want to find out if the medicine called melatonin helps children to sleep better during the night than a placebo medicine. A placebo is a dummy capsule that looks the same as the melatonin, but contains no medicine.

Doctors give melatonin to lots of children to help them sleep at night. But we do not know for sure that it works. We also want to see how much you need to make you sleep better by increasing the amount we give you each week. We hope that the results of this research will help us to treat other young people better.

What is the medicine, device or procedure that is being tested?

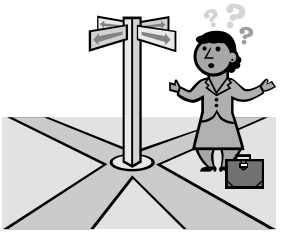
The medicine we are testing is called melatonin; it is normally found in your body and increases in the dark to help you sleep. The melatonin in your body might not work very well or you might not have enough of it so you have problems sleeping at night.

The melatonin used in this project has been made especially for the study. Half of the children in the study will be given the melatonin and the other half will be given the placebo medicine. You and your parents will not be able to choose which medicine you take and you will not know which medicine you are taking. Your doctor and nurse will not know which medicine you are given, but they can find out if they need to.

Why have I been asked to take part?

You have been chosen because you have problems sleeping, this project will involve about 200 children from England.

Do I have to take part?



No – not at all. It's completely up to you! We only want people to take part if they want to. Just tell us if you don't. Whatever you decide nobody will mind, and it will not affect how you are looked after. If you decide to take part and then change your mind, that's OK too. You can stop at any time and you don't have to give a reason.

If you agree to take part, we will ask you to write your name on a form called an 'assent form'. This is to say you understand the study and what will happen. You will be given your own copy of this form to keep as well as this information sheet.

Your study doctor or nurse may ask if you mind them recording them talking to you about the study. This is because a study called RECRUIT is being done to find out what it is like for parents and children when they are asked to take part in a study. If you agree, the study doctor or nurse will give your contact details to the researchers running the RECRUIT study. The RECRUIT researchers might then contact you to ask some more questions. If you decide you do not want anyone to listen to the recording, that is OK too, and it will be deleted.

What will happen to me if I take part and how long will it take?

If you take part you will be involved in this study for 16 weeks. During this time you will visit the hospital 3 times. The study nurse will also visit you and your family at home and speak to your parents on the telephone.

At your first visit to the doctors, you and your parents will meet the study nurse. If you say yes to joining the study, you will need to answer some questions and the doctor will look you over to check you are well enough to be in the study.

The nurse will give your parents some ideas to help you sleep better. They will use these for the next 4 weeks. We would like you to wear a special watch for these 4 weeks that tells us when you fall asleep, when you get up in the morning and whether you wake up during the night.

After 4 weeks you and your parents will go back to the doctor. If it is still OK for you to be in the study and you still want join in your parents will be given your medicine. We will ask you to write on another assent form to say that you are happy to carry on doing this research.

We would like you to wear the special watch again for 1 week later in the study.

You will need to take 1 capsule of your medication every night before you go bed for 12 weeks. If you cannot swallow it your parents can mix the medicine in some water, orange juice, milk, strawberry yogurt or strawberry jam.

On 2 days during the study we want to measure how much of the medicine is in your body. We do this by asking you to spit into a container if you can. If you can not spit into the container your parents can wipe a small sponge on a stick around your mouth to soak up your spit. This gives us a sample of your saliva and we measure the amount of melatonin in it. You will need to do this every hour from 5 o'clock in the afternoon until you go to bed. Each container will be placed in a freezer until we test it.

At the end of 12 weeks you and your parents will visit the doctor again and you will need to answer some questions. The doctor will check that you are well in the same way he or she did at the beginning of the study.

What will I be asked to do?

During the study you will need to:

- go to the hospital 3 times during the 16 week study.
- let the doctor look you over to check you are well at the beginning and end of the study.
- take 1 capsule every night before bed for 12 weeks.
- keep taking your normal medicines
- give a saliva sample every hour from 5 o'clock in the afternoon until bedtime on 2 different days.

What other treatment could I have instead?

Your doctor or nurse might give your parents some information on ideas that might help you fall asleep or stop you waking up so much in the night. They might give you melatonin to help you sleep, but you would not be given a dummy medicine.

What are the side effects of the medicines and might I have some if I take part in the research?

Sometimes medicines upset our body and if this happens we call them side-effects. Melatonin has been given to lots of children before and from this we think that side-effects do not happen very often. A few people who take melatonin may get these side-effects

- sleepiness
- rashes
- coughing
- increased fits if they have epilepsy

Is there anything else to be worried about if I take part?

People sometimes worry about whether the things they say will be kept private. In this study the only time we would ever tell somebody what you have said is if something made us concerned about you and your safety. Apart from that, everything you tell us is private.

If we think you are old enough we might ask you to take a pregnancy test before you start the study. This is because melatonin might harm babies before they are born. You can say no to this test if you don't want to have it.

If you become pregnant during the study you need to tell your doctor or nurse immediately. They will check you and your unborn baby are healthy.

How will the information about me be kept private?

When we write down information you or your parents tell us we will give you a number. We will use this number instead of your name so no-one will know the information is about you. Of course you can tell your family and friends about it if you want to. When we have finished the study we will write reports about it, but these reports won't have your name on them.

What are the possible benefits of taking part?

We cannot promise the study will help you but the information we get might help treat other young people who have problems sleeping.

Who can I contact for further information?

If you have any questions at all, at any time, please contact: study nurse name, telephone and email.

The other people helping with this study are:

Thank you for reading so far – if you are still interested, please go to Part 2:

Part 2 - more detail – information you need to know if you still want to take part.

What happens when the research project stops?

When all the children have finished the study you will be told whether you were taking the melatonin or the placebo.

What happens if new information about the research medicine comes along?

Sometimes during research, new things are found out about the research medicine. Your doctor will tell you all about it if this happens. What is best for you might be:

- To carry on taking part in the study
- To stop taking part and go back to your usual treatment

What if there is a problem or something goes wrong?

If you have a question about any part of the study, you should ask the researchers who will do their best to answer your questions (see contact details on page 5). If you are still unhappy and wish to complain to someone else, you can do this using the NHS Complaints Procedure. You might need to ask your family to help you with this.

Will anyone else know I'm doing this?

Yes –

- The researchers who are running the study or research inspectors might want to see your medical notes to make sure the research is being done properly.
- Your family doctor will be told you are taking part

If you agree to take part in the research, any of your medical records may be looked at to check that the study is being done properly. So that we can check you agreed to join in the study a copy of the forms you and your parents wrote on will be sent to the Clinical Trials Unit (CTU) who are running the study. The CTU will not tell anyone else your name and the form will be kept in a locked cupboard.

What will happen to any samples I give?

Saliva samples will be taken to measure melatonin levels in your body. This test would not normally be done. These samples will be sent to a laboratory outside of the hospital. They will not have your name on them so no-one will know they are your samples.

What are genetic tests and will any be done?

We would like to collect a genetic sample from all the children in the study. This is an extra study and you do not have to give us the sample. This sample is also saliva. You can still take part in the main study, even if you say no to this part. Another information sheet explains this part of the study. If you say yes you will need to write your name on another 'assent form' to tell us you understand what will happen to you and are happy to do this.

Who is organising and funding the research?

The NHS Health Technology Assessment Programme has provided the money to carry out this study. Alliance Pharmaceuticals are providing the money for the study treatments. The Alder Hey Children's NHS Foundation Trust and the University of Liverpool are organising the study.

Who has reviewed the study?

Before any research goes ahead it has to be checked by an Ethics Committee. The Ethics Committee is a group of experts and ordinary people who look at all research studies very carefully. The Committee decide whether the study is OK to do. Your project has been checked by the North West Multi-centre Research Ethics Committee.

Thank you very much for taking the time to read this. Please ask any questions if you need to.

ASSENT FORM FOR CHILDREN Version 2.0 Date 27/01/09
(to be completed by the child and their parent/guardian)

MENDS: The use of MElatonin in children with Neuro-developmental Disorders and impaired Sleep

Child (or if unable, parent on their behalf) /young person to circle all they agree with please:

Have you read information (or had read to you) about this project?	Yes/No
Has somebody else explained this project to you?	Yes/No
Do you understand what this project is about?	Yes/No
Have you asked all the questions you want?	Yes/No
Have you had your questions answered in a way you understand?	Yes/No
Do you understand it's OK to stop taking part at any time?	Yes/No
Are you happy to begin this study?	Yes/No/Not applicable (T0)
Are you happy to continue with this study?	Yes/No/Not applicable (T-4)

If any answers are 'no' or you **don't** want to take part, **don't** sign your name!

If you do want to take part, please write your name and today's date

Your name _____

Date _____

Your parent or guardian must write their name here too if they are happy for you to do the project

Print Name _____

Sign _____

Date _____

The researcher who explained this project to you needs to sign too:

Print Name _____

Sign _____

Date _____

Thank you for your help.
When completed, 1 for patient; 1 for researcher site file; 1 for MCRN CTU, 1 (original) to be kept in medical notes

(To be presented on local headed paper and include MENDS logo)

Centre Name and Number: xxx

Childrens (5 to 10 years equivalent) Information and Consent Form
Version 2.0 Date 27/01/09

MENDS: The use of MElatonin in children with Neuro-developmental Disorders and impaired Sleep

We thank your mum or dad for helping you to read this information

What is a study? Why is this study being done?

A research study is what you do when you want to learn about something or find out something new. It can help doctors and nurses and other people in the hospital find out which medicines can help children get better.

This study is to see if the medicine called melatonin helps you sleep better than the placebo medicine. A placebo is a dummy capsule that looks the same as the melatonin, but contains no medicine.

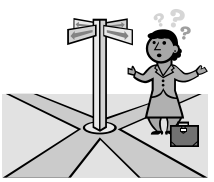
Why have I been asked to take part?

You have been asked to take part because you have trouble falling asleep at bedtime or because you wake up lots of times in the night.

Did anyone else check the study is OK to do?

Before any study is allowed to happen, it has to be checked by a group of people called an Ethics Committee. The Ethics Committee is a group of experts and ordinary people who look at studies very carefully to decide whether they are OK to do. The North West Multi-centre Research Ethics Committee have looked at this study and decided it is OK.

Do I have to say yes?



No – not at all. It's up to you. Just say if you don't want to take part. Nobody will mind.

If you do take part, you will need to write your name on a form called an 'assent form'. This form is to say that you understand the study and what will happen if you take part. You will be given your own copy of this form to keep, as well as this information sheet.

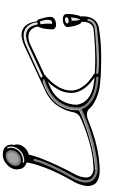
Your study doctor or nurse may ask if you mind them recording them talking to you about the study. This is because a study called RECRUIT is being done to find out what it is like for parents and children when they are asked to take part in a study. If you agree, the study doctor or nurse will give your contact details to the researchers running the RECRUIT study. The RECRUIT researchers might then contact you to ask some more questions. If you decide you do not want anyone to listen to the recording, that is OK too, and it will be deleted.

What will I need to do and how long will it take?

At your first visit to the doctors, you and your parents will meet the study nurse. If you say yes to joining the study, you will need to answer some questions.

The doctor will check you are well enough to be in the study by:

- looking at your arms and legs to see how strong you are
- asking you to pull some funny faces
- feeling your tummy
- listening to your chest with a stethoscope



The nurse will give your parents some ideas to help you sleep better. They will use these for the next 4 weeks. We would like you to wear a special watch for these 4 weeks that tells us when you are asleep and when you are awake.

After 4 weeks you and your parents will go back to the doctor. If it is still ok for you to be in the study and you still want to join in your parents will be given your medicine. We will ask you to fill in another assent form to say that you are still happy to join in.

Half of the children in the study will be given melatonin and the other half will be given the placebo medicine. You will not be able to choose which one you will get. You will not be told which one you are taking. Your doctor and nurse will not be told which one you are taking, but they can find out if they need to.

We would like you to wear the special watch again for 1 week later in the study.

You will need to take 1 capsule of your medicine every night before you go to bed for 12 weeks. If you cannot swallow it your parents can mix the medicine in some water, orange juice, milk, strawberry yogurt or strawberry jam. During this time the study nurse will come and see you at home to check you are ok. The study nurse will also speak to your parents on the telephone to make sure you are ok.

Your body makes its own melatonin and the amount can be measured by testing the spit (saliva) from your mouth. On 2 days during the study we want to measure how much melatonin is in your body. We do this on evenings when you won't take the study medicine. We will ask you to spit into a container if you can. If you can not spit into the container your parents can wipe a small sponge on a stick around your mouth to soak up your spit. This gives us some of your saliva and we measure the amount of melatonin in it. You will need to do this every hour from 5 o'clock in the afternoon until you go to bed. Each container will be kept in the freezer until we test it.

At the end of 12 weeks you and your parents will visit the doctor again andyou will need to answer some questions. The doctor will check that you are well in the same way he or she did at the beginning of the study.

Will the medicine upset me?

Sometimes medicines upset our body and if this happens we call them side-effects. Melatonin has been given to lots of children before and from this we think that side-effects don't happen very often but a few people who take melatonin get these side-effects

- sleepiness
- rashes
- coughing
- increased fits if they have epilepsy

Will joining in the study help me?

We cannot promise the study will help you. In the future the information we get from this study might help other boys and girls with problems sleeping.

Is there another sort of treatment I can have instead?

Your doctor or nurse might give your parents some information on ideas that might help you fall asleep or stop you waking up so much in the night. They might give you melatonin to help you sleep, but you would not be given a placebo medicine.

Who will know that I am in the study?

The doctors and nurses who normally take care of you will know. So will the study nurse and the study pharmacist.

How will the information about me be kept private?

Everything you tell us is private. The only time we would ever tell somebody what you have said is if something made us worried about you. All information collected for this study will be kept safely on the computer or as paper records. Of course, you can tell your family and friends about the study if you want to.

What happens when the research stops?

When all the children have finished the study you will be told whether you were taking the melatonin or the placebo.

What happens if a better medicine comes along?

Sometimes during research, new things are found out about the research medicine. Your doctor will tell you all about it if this happens. What is best for you might be:

- To carry on taking part in the study
- To stop taking part and go back to your usual treatment

What happens if there is a problem with the study?

If you think there are any problems with the study or if you have any worries about it you can tell your parents. You can also tell the study nurse (her name is at the end of this leaflet). They will do their best to answer your questions. If you are still unhappy you can talk to someone else. Your parents will probably be the best people to talk to.

What if I don't want to do the study anymore?

If you want to stop the study at anytime, just tell your parents, doctor or nurse. They will not be cross with you. If you say no or want to stop the study at any time it will not change the way the doctors and nurses will look after you. Your doctor will choose which treatment is best to use instead.

What will happen to the results of the study?

We will write reports for the doctors and nurses who see children with sleep problems. The results will also be written in special magazines (scientific journals). No-one will know that they are your results because your name will not be written on them. We will send you a report telling you the results at the end of the study if you would like us to.

What shall I do now?

Now you know about the study you need to think about whether you want to join in or not.

Who is running the study?

If you have any questions at all, at any time, please contact: study nurse name, telephone and email.

The other people helping with this study are:

Research Doctor:

Thank you very much for taking time to read this. Please ask any questions if you need to.

ASSENT FORM FOR CHILDREN Version 2.0 Date 27/01/09
(to be completed by the child and their parent/guardian)

MENDS: The use of MElatonin in children with Neuro-developmental Disorders and impaired Sleep

Child (or if unable,parent on their behalf) /young person to circle all they agree with please:

Have you read information (or had read to you) about this project? Yes/No

Has somebody else explained this project to you? Yes/No

Do you understand what this project is about? Yes/No

Have you asked all the questions you want? Yes/No

Have you had your questions answered in a way you understand? Yes/No

Do you understand it's OK to stop taking part at any time? Yes/No

Are you happy to begin this study? Yes/No/Not applicable (T0)

Are you happy to continue with this study? Yes/No/Not applicable (T-4)

If any answers are 'no' or you **don't** want to take part, **don't** sign your name!

If you do want to take part, please write your name and today's date

Your name _____

Date _____

Your parent or guardian must write their name here too if they are happy for you to do the project

Print Name _____

Sign _____

Date _____

The researcher who explained this project to you needs to sign too:

Print Name _____

Sign _____

Date _____

Thank you for your help.
When completed, 1 for patient; 1 for researcher site file; 1 for MCRN CTU, 1 (original) to be kept in medical notes

(To be presented on local headed paper and include MENDS logo)

Centre Name and Number: xxx

Additional Young Persons Information and Consent Form for Genetic Study
Version 1.1 Date 03/12/07

MENDS: The use of MElatonin in children with Neuro-developmental Disorders and impaired Sleep; a randomised, double-blind, placebo-controlled, parallel study

What is the purpose of the research project?

Your body is made up of millions of cells and they contain coded messages called genes. Genes tell your cells how to develop. Some features that are controlled by your genes are easy to see, like your hair and eye colour. Other features are not so easy to see, like how your body responds to medicines. Genes are passed on from parent to child. The study of genes is known as genetics.

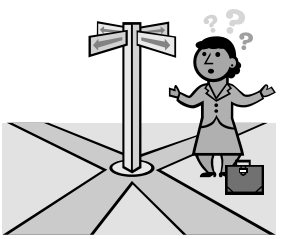
Melatonin is made by your body and helps control when you sleep and wake. We already know that the amount of melatonin your body makes and releases is controlled by your genes.

No one gene has been found that controls melatonin release but we have some idea of which genes might be involved.

Melatonin medicine doesn't work for everyone so we also want to see if this is linked to genes.

Do I have to take part?

No – not at all. It's completely up to you! We only want people to take part if they want to. Just tell us if you don't. Whatever you decide nobody will mind, and it will not change how you are looked after. You can say no to this part of the study and still do the main study.



If you decide to take part and then change your mind, that's OK too. You can stop at any time and you don't have to give a reason.

If you take part, we will ask you to write your name on a form called an 'assent form'. This is to say you understand the study and what will happen. You will be given a copy of this form to keep as well as this information sheet.

What will happen to me if I take part?

If you take part in the study, the research nurse will take a sample of saliva from you so that we can look at the genes. The nurse will gently wipe the inside of your mouth with a small sponge on the end of a spatula to collect the saliva.

What do I have to do if I agree to take part?

Let the study nurse take a sample of saliva (spit) from you.

What are the possible disadvantages and risks of taking part?

There are no problems with having this done.

What are the possible benefits of taking part?

This part of the study will not help you. It will help us to understand how genes are linked to sleep problems and melatonin levels. This might help us to find a test we can use in the future to see if melatonin treatment will help a child before we give it to them.

Will my taking part in the study be kept private?

When we write down information you or your parents tell us we will give you a number. We will use this instead of your name so no-one will know the information is about you. Of course you can tell your family and friends about it if you want to. When we have finished the study we will write reports about it. We will use the number we have given you and not your name.

What will happen to any samples I give?

Your sample will be sent to a laboratory outside of the hospital. It will be labelled with a number instead of your name. No-one will know it is your sample. You will not be able to get results from this extra test.

Who do I contact for more information?

If you have any questions at all, at any time, please contact: study nurse name, telephone and email.

The other people helping with this study are:

Research Doctor:

Thank you very much for taking the time to read this. Please ask any questions if you need to.

ASSENT FORM FOR CHILDREN Version 1.1 Date 03/12/07
(to be completed by the child and their parent/guardian)

MENDS: The use of MElatonin in children with Neuro-developmental Disorders and impaired Sleep

Child (or if unable,parent on their behalf) /young person to circle all they agree with please:

Have you read information (or had read to you) about this project? Yes/No

Has somebody else explained this project to you? Yes/No

Do you understand what this project is about? Yes/No

Have you asked all the questions you want? Yes/No

Have you had your questions answered in a way you understand? Yes/No

Do you understand it's OK to stop taking part at any time? Yes/No

Are you happy to take part? Yes/No

If any answers are 'no' or you **don't** want to take part, **don't** sign your name!

If you do want to take part, please write your name and today's date

Your name _____

Date _____

Your parent or guardian must write their name here too if they are happy for you to do the project

Print Name _____

Sign _____

Date _____

The researcher who explained this project to you needs to sign too:

Print Name _____

Sign _____

Date _____

Thank you for your help.

When completed, 1 for patient; 1 for researcher site file; 1 for MCRN CTU, 1 (original) to be kept in medical notes

Appendix C: GP Letter

(To be presented on local headed paper)

Centre Name and Number (if applicable): xxx

GP Letter Version 1.0 Date 26/04/07

MENDS: The use of MElatonin in children with Neuro-developmental Disorders and impaired Sleep; a randomised, double-blind, placebo-controlled, parallel study

ISRCTN05534585

Dear Dr _____,

Following fully informed written consent of their parent/legal guardian, your patient, _____ (date of birth: dd/mon/yyyy), has been entered into the above trial.

The aim of this randomised, parallel, double-blind, placebo-controlled, multi-centre clinical trial is to confirm (or refute) that immediate release melatonin is beneficial in improving total duration of night-time sleep and can reduce the time taken to fall asleep in children with neuro-developmental disorders.

Please find enclosed a copy of the patient information sheet for your information.

You will be kept up to date with your patient's progress but if you have any concerns or questions regarding this study please contact the responsible doctor:

Dr _____ at _____(Hospital)

Tel: _____

Yours sincerely,

<<Name>>
<Position>>

Appendix D: Instructions for Collection of Salivary Samples (for parents)

UniS
University of Surrey
School of Biomedical and Molecular Sciences

Instructions for Collection of Saliva Samples Version 2.0 Date 17/08/07

You should have been given

- 10 tubes, 5 packs of sponges and 1 pair of scissors – each tube should have your child's code and approximate times to take the sample and a space for you to fill in the exact time labelled on it
- labelled grip seal bags
- 2 saliva sample collection record sheets

Saliva samples should be collected on TWO different occasions –

1. The evening before your second clinic visit
2. The evening after the week 10 telephone call (your study nurse will remind you when she calls)

On both occasions we would like you to collect saliva samples approximately every hour from 5:00 pm to bedtime. Don't disturb your child and try to take more samples after you have snuggled them down in bed.

During this period we would ask you to ensure your child:

1. remains indoors and as quiet as possible (seated, lying down) in a dimly light room (e.g. a single table lamp on one side of the room, avoid being close to the window).
2. does not drink caffeinated drinks (e.g. coca cola, tea or coffee) from 1 pm (lunchtime) on the day of collection.
3. every hour collect a saliva sample into the appropriately labelled collection tube. The MENDS nurse will have chatted to you about the different ways of collecting the spit (saliva) and you should have also had a chance to practise this already.

   First remove the cap from the plastic tube and then either:

   a) Ask your child to spit into the tube. We need 2mls which is slightly less than half a teaspoon. This is the absolute minimum and more is even better.

   OR

   b) Place one of the saliva sponges in the child's mouth in the *cheek pouch* (the space between the gums and the inner cheek). Gently move the saliva sponge around the upper and lower cheek pouches on one side of the mouth to soak up as much saliva as possible. There is no need to 'scrape' the inner cheek with saliva sponges – simply collect as much saliva as possible from the cheek pouches. The sponge will absorb more saliva if it is left in the child's mouth for a longer time (up to 60 seconds). Once collected cut the sponge into the tube provided and seal the lid. Recycle/discard the plastic handle.

   Repeat this process with a second sponge on the other side of the mouth.

   It might be helpful to practice collecting saliva at the same time you clean your child's teeth. This can make it more familiar and more fun.
4. record the time of the saliva collection on the form provided.
5. place the tube in the grip seal bag provided and put this into the freezer (domestic freezer is fine/freezer box is also OK if it is cold enough to freeze food) after the saliva sample has been collected (within 10 minutes of collection).

Should your child wish to go to the toilet or move about, please do so immediately after collection of a sample and try to ensure the child is still and seated again 15 mins before the next sample is due to be collected. Should your child wish to eat or drink (only non-caffeinated drinks), they should rinse their mouth out with water as soon as they have finished. Please try to avoid rinsing with water close to the time of saliva collection (as this may dilute the saliva sample).

1. store saliva samples in the grip seal bag in your freezer/freezer box.
2. your MENDS nurse will have arranged with you collection of the sample.

Appendix E: Instructions for Collection of Salivary Samples (for researchers)

MENDS Storage and Transport of Saliva Samples Version 1.0 26/04/07

Saliva samples should be collected in the participants' homes as per instructions (see Appendix D). Once the saliva samples have been collected into the tubes, they should be put immediately into a domestic freezer (within 10 minutes of sample collection).

For transport of saliva samples from participants' homes by the researcher, this should be done with ice packs in cool bags/igloo polystyrene boxes (taking care that the samples do not thaw during transport). This can be done in one batch for each participant at the end of the 16 week study period.

An intermediate hospital lab freezer will be needed to store samples (-20 or -70 are fine)

Then transport samples in one batch at end of study from central collection points to the University of Surrey. This should be done by courier on dry ice (e.g. TNT courier service provide this service). Samples should be delivered to:

Dr Benita Middleton
Senior Research Fellow
School of Biomedical & Molecular Sciences
University of Surrey
GUILDFORD
Surrey GU2 7XH

Tel/fax: 01483 689712
Email: b.middleton@surrey.ac.uk

Samples should be identified with a unique participant code. Paper records/files will be kept in a locked office. Samples will be stored in a padlocked freezer in a padlocked laboratory (21AY02).

Assay of Saliva Samples

Saliva samples will be thawed and assayed for melatonin using a standard protocol (Appendices 2 and 3). All samples for a single participant will be measured in the same assay (samples will be measured in duplicate).

Appendix F: Salivary Melatonin Assay Protocols

STOCKGRAND LTD.

School of Biomedical & Molecular Sciences
University of Surrey
Guildford, Surrey GU2 7XH, UK
Tel: (0)1483 689712
Fax: (0)1483 689712/576978
VAT Registration no: GB 529 0040 74
e-mail: Stockgrand@surrey.ac.uk

(i) RABBIT ANTIBODY TO MELATONIN

Product Reference no: R/R/19540-16876

Catalogue nos: AB/R/03 (sufficient for 4000 assay tubes)

AB/R/031 (sufficient for 150 assay tubes)

Antiserum
The antiserum was raised in a rabbit to melatonin conjugated by glutaraldehyde reduction through the 2 position to human serum albumin.

Specificity
The antiserum is sufficiently specific for clinical application in saliva without pre-assay treatment. It can be used for assaying melatonin levels in human plasma, but pre-extraction is necessary.

Relative specificity

	% cross reactivity
Melatonin	100
6-hydroxymelatonin	5.333
6-sulphatoxymelatonin	0.229
N-acetyl-5-hydroxytryptamine	0.084
N-acetyl-tryptamine	0.080
5-hydroxy-indole acetic acid	0.005
5-methoxytryptamine	<0.003
5-hydroxytryptamine	<0.003
N-acetyltryptophan	<0.003
5-methoxytryptophol	<0.003
Tryptophan	<0.0003

Sensitivity
The lower limit of sensitivity is 2pg/ml using the recommended procedure.

Assay procedure

The assay is direct. Saliva is incubated with the first antiserum and ^{125}I-melatonin overnight at 4^{o}C. Normal rabbit serum, donkey-anti-RABBIT antiserum and 6% polyethylene glycol are added after an incubation of 4hr the tubes are centrifuged, the supernatant discarded and the pellet counted in a gamma counter.

A solid phase separation system may also be used, and the first incubation time decreased to 4hr. Using this method samples may be assayed within a working day.

Standards are also assayed and the data used to construct a standard curve which covers the range 0 - 100pg. Melatonin concentrations in the saliva samples are then calculated from this curve. A detailed protocol is provided with the antiserum.

Assay Requirements

Assay buffer: Tricine buffer (pH 8.0) with gelatin. Tricine is available commercially (Sigma Ltd.).

Radioligand: ^{125}I-melatonin is available commercially (Amersham International).

Standards: Melatonin is available commercially (Sigma Ltd).

Equipment:

In addition to standard laboratory equipment a refrigerated centrifuge and a gamma radiation counter are required.

(ii) INSTRUCTIONS FOR DIRECT RADIOIMMUNOASSAY OF MELATONIN IN HUMAN SALIVA USING AN ^{125}I - LABELLED TRACER

The RIA of melatonin has been modified from Fraser et al (1983) to use an iodinated tracer and antiserum raised against melatonin conjugated at the 2 position. Salivary melatonin levels measured in this way correlate well with levels measured by extraction and provide a sensitive rapid and economical assay. The antibody bound and free fractions can be separated by using either solid or liquid phase separation system. Using a solid phase system the assay can be completed within one day.

REAGENTS

All water used is freshly double glass distilled (DGDW).

Buffer: tricine (Sigma Ltd product no.: T0377) is made up at 0.1M, pH 8.0 with 0.9% NaCl and 0.2% gelatin. Heat to 50^{o}C for 30min to dissolve the gelatin.

17.9g tricine	)
9.0g NaCl	) to 1l with DGDW
2.0g gelatin	)

Bring to pH 8.0 with 1M NaOH
Buffer is stored at 4^{o}C and made up fresh weekly.

Antiserum: rabbit anti-melatonin antiserum (code no. R/R/19540-16876) is supplied freeze dried.

AB/R/03 - 133μl of a 1/10 dilution (sufficient for 4,000 assay tubes).
The contents of the vial should be reconstituted with 2ml DGDW and 50μl aliquots stored at -20°C. The working dilution sufficient for 100 assay tubes is prepared by diluting a 50μl aliquot to 10ml with assay buffer.

AB/R/031 - 50μl of a 1/100 dilution (sufficient for 150 assay tubes).
The contents of the vial should be reconstituted with 15ml assay buffer and are sufficient to add 100μl to each of 150 assay tubes.

These working dilutions are prepared fresh daily. However it may be necessary to assess the antiserum dilution appropriate to your label by performing conventional antiserum dilution curves.

^{125}I-melatonin tracer: this tracer is available from Amersham International

Double antibody separation system

a) solid phase separation system

A second antibody raised against rabbit IgG and linked to a suitable solid phase

Dapsep can be obtained from us in amounts sufficient for either 150 (SP/DR/01) or 1000 (SP/DR/02) assay tubes.

Brij / saline wash solution: dissolve 9g NaCl in 998ml DGDW and add 2ml Brij 35.

b) liquid phase separation system

i) normal rabbit serum diluted 1:200 in assay buffer
ii) donkey anti-rabbit IgG suitably diluted in assay buffer
iii) 6% polyethylene glycol 6000 "PEG" in DGDW

Standards: melatonin (Sigma Ltd product no.: M5250) stock solution is made up at 1mg/ml by dissolving 10mg melatonin in 0.5ml absolute ethanol and adjusting the volume to 10ml with DGDW. This solution is stable for at least a year at 4°C. The working standard is freshly prepared daily from this ethanolic stock as follows:

100μl (1mg/ml) to 100ml in DGDW = 1μg/ml
500μl (1μg/ml) to 50ml in DGDW = 10ng/ml
50μl (10ng/ml) to 2.5ml in assay buffer = 0.2ng/ml

Further dilutions with assay buffer provide a standard curve as follows:

MT standard 0.2ng/ml	Assay buffer	MT pg / tube	MT pg/ml
0	500	0	0
5	495	1	2
10	490	2	4
25	475	5	10
50	450	10	20
125	375	25	50
250	250	50	100
500	-	100	200

The standards are treated in exactly the same way as the saliva samples in the assay.
Saliva samples: samples are stored at -20°C until assayed.

METHOD

Duplicate tubes are set up for all samples, standards, total radioactivity tubes and non-specific binding tubes. The volumes required for the assay are as follows:

Sample / standard	500µl
Antiserum	100µl
Radiolabel	100µl

Solid phase separation		**Liquid phase separation**	
Double antibody / solid phase	100µl	Double antibody	100µl
		Normal rabbit serum	100µl
Brij saline wash	1000µl	6% PEG 6000	500µl

The volumes are added with ordinary microlitre dispensers or repeating dispensers.

ASSAY PROTOCOL

1. Pipette standards and buffer to form standard curve

2. Add 500µl saliva samples to assay tubes

3. Add 100µl of diluted antiserum to all tubes except totals and NSBs. Vortex and incubate at room temperature for 30 minutes

4. Add 100µl ^{125}I-melatonin and vortex. Incubate at 4^{o}C for 15 - 18 hours.

If a solid phase separation system is used this incubation time can be decreased to 4 hours at room temperature

EITHER:

5. Solid phase separation system. Add 100µl solid phase double antibody and incubate for 1h at room temperature with intermittent mixing. Add 1ml Brij / saline wash and centrifuge at room temperature at 1500g for 10 minutes.

OR:

5). Liquid phase separation system. Add 100µl diluted double antibody, 100µl diluted normal rabbit serum and 500µl 6% PEG solution. Mix and incubate at 4^{o}C for 4 hours. Centrifuge at 3000g for 20 minutes.

6). Decant over a mesh and discard supernatant. This must be done immediately after centrifugation. (An aluminium or Teflon covered mesh is placed over the rack of tubes, and the whole carefully inverted over a sink to remove supernatant. The whole assembly is then blotted with absorbent paper to remove final drips before righting the rack).

7). Count the pellet in an appropriate gamma radiation counter. Determine the melatonin concentration from the dose response curve.

REFERENCE

English J, Middleton BA, Arendt J & Wirz-Justice A. Ann Clin Biochem 30, 415-416 (1993).

Appendix G: Drug Shipment Request Form

MENDS Shipment Request Form Version 1.1 17/08/07	**Order No:** _____
MENDS *STUDY NO:* **05/14/02 / Eudract 2006-004025-28**	
INVESTIGATOR SITE – REQUEST DETAILS	
Please supply the following Medication**:** Description of Supplies: Quantity : Include Temperature Monitor: No Initial or Follow Up: Site Regulatory Approval in Place: Yes / No*	
Centre Name and Number	
Investigator *(enter name of Principal Investigator)*	
Date medication is required (approx. delivery time) *Enter date and if possible time of delivery required*	
Delivery contact (CONSIGNEE) Name of Pharmacist +phone number of recipient + fax number of recipient	Name: Tel: Fax:
Delivery address: (Give full details including department and ward of hospital – or pharmacy location – as appropriate)	
Requested by: NB: Signature confirms that all regulatory approvals for the investigator site requested are in place and that shipment may proceed.	Signature / Date: _____ Print Name: _____ Authority: _____ Tel No: _____Fax-No.:_____
Please Fax to Penn Pharmaceuticals at FAX-No: +44 (0) 1495 713743 For the attention of: Sue Court	
PENN PHARMACEUTICALS – DESPATCH DETAILS	
Material despatched as requested above: Kit Numbers despatched:	
No of shipment cartons	
Temperature Monitor Included: Y / N *	
Courier: Consignment Note No.:	
Despatched By: (Initials / Date)	
Checked By: (Initials / Date) Supervisor	
Date shipped	
On despatch, fax to **Client:** _____ **Consignee:** _____	
CONSIGNEE – Acknowledgement of receipt	
Drug supplies received complete and in good condition Y / N * * Circle as appropriate Package is unopened and undamaged Y / N * Confirm Temperature Monitor within specified range Y / N / NA * (NB: Please fax print-out to Penn Pharmaceuticals) Ensure that drug supplies are stored at _____ °C and under appropriate conditions	
Consignee (Signature / Date) Recipient to sign and date	
Please fax completed form to **PENN Pharmaceuticals –FAO: Sue Court Fax.No: +44 (0) 1495 713743**	

Appendix H: Nurses Script for handing over the sleep hygiene booklet

Version 1.0 26/04/07

General Points

- Bold headings are intended to be reminders of the general focus of the following paragraphs and what needs to be said and conveyed to parents.
- All points in italics are intended to be spoken to the parents by the nurses.
- Deliver with enthusiasm, belief in the ideas and a conviction that the booklet will be able to make things better for most! Nurses need training in this.

Introduction to the booklet/contents

This booklet contains ideas for how you can help to teach your child to settle off to sleep and sleep through the night in their own bed. Not every section may be relevant for you and your child but it's a good idea to read the whole booklet.

Walk through the booklet probably no more than one minute to point out what it contains

Page 3 contains information on sleep problems, and then there is a section describing the techniques in general, followed by specific advice about how to set up a bedtime routine. On page 7 there is a section on how to change the time when your child sleeps. There are pieces on settling your child to sleep, dealing with nightwaking and resettling your child to sleep. Then comes the matter of how to handle children who want to sleep in your bed.

Most of the techniques described in the booklet emphasise rewarding good behaviour, so there is information about that on page 14. There is advice on daytime napping followed by a summary page at the end.

These techniques <u>are</u> useful

The scientific research that has been done so far suggests that the techniques described in this booklet have been shown to be the best way to help children with learning disabilities to sleep better. For some children they have been shown to completely resolve the problem; for others to improve things – they may not be a total cure but they are likely to make things a lot better for most children.

Sleep is, in large part, a learnt behaviour

The techniques are based on the idea that whilst some aspects of sleep are controlled by our bodies and brains, other parts are controlled by how we have learnt to sleep and where and when.

For instance, if I asked you to lie down on the kitchen floor in the middle of the morning and go to sleep, you might find it more difficult than in your comfy bed at night because we learn to associate particular places, times and so on with sleep…

Not parents fault

Just because your child may need extra help to learn how to sleep doesn't mean that it is your fault that they haven't learnt how to do it 'right' so far. Some children learn at different rates/times etc. Success with the techniques doesn't mean that you have 'done things wrongly' before - the important thing is that you can use these techniques to help.

Previous experiences

You might have read about these techniques or even tried them before. Don't dismiss them just because you have used them unsuccessfully in the past. The techniques can work very differently at different times (e.g. your child may be older and able to learn more now, the situation might be different now (for you or your child) and this can affect how successful the techniques are). Give them a go- you have nothing to lose and everything to gain.

Implementing ideas #1 (doing things sequentially)

If your child has many problems with sleep you don't need to tackle everything at once. You can tackle one problem at a time.

Example – child who won't go to sleep without a parent present and falls asleep too late (e.g. first get a bedtime routine going, then teach your child to settle to sleep alone, then move the times that your child sleeps).

Implementing ideas #2 (being consistent)

Perhaps the most important thing you can do when trying to teach your child a new behaviour is to be persistent and to use repetition. We all learn most quickly if the rules are consistent (e.g. if you get caught for speeding every time you drive fast you are less likely to do it than if you only get caught sometimes!) The more you keep doing the same thing over and over the easier it will be for your child to learn a new set of behaviours.

Implementing ideas #3 (things may get worse first)

It's also important to remember that if you start using these techniques your child's sleep behaviour may get worse before it gets better – this is because your child will be 'testing' out the new set of rules. So, if your child's sleep behaviour gets worse for a few days don't be discouraged. Quite the opposite; feel glad as this shows that your child has noticed that 'something' has changed. This is the first step in learning a new behaviour.

Understanding

As part of this research project, we can't give you any extra advice over and above the information in the booklet. However, if anything in the booklet is not clear or you are not sure that you understand something please feel free to give me a ring on (telephone number).

Appendix I: Drug Accountability Log

MENDS Treatment Accountability Log
Version 2.1 031207

Centre Number: _ _ _
Registration Number _ _ _ _ _ _

Randomisation Number _ _ _ _ _ assigned by _____ checked by _____
Sign and date Sign and date

Batch Number _ _ _ _

For each visit, please complete the quantity of capsules dispensed and the quantity of capsules returned.

Visit	Strength	0.5mg	2 mg	6 mg	12 mg	Current Dose	Pharmacy Signature	Date dd/mm/yyyy	RP Signature	Date dd/mm/yyyy
T0W	Quantity of capsules issued	14								
	Quantity of capsules returned	0				0.5 mg				
T+1W	Quantity of capsules issued	7	14							
	Quantity of capsules returned									
T+2W	Quantity of capsules issued									
	Quantity of capsules returned									
T+3W	Quantity of capsules issued									
	Quantity of capsules returned									
T+4W	Quantity of capsules issued									
	Quantity of capsules returned									
T+5W	Quantity of capsules issued									
	Quantity of capsules returned									
T+6W	Quantity of capsules issued									
	Quantity of capsules returned									

At T0, 14 x 0.5mg capsules will be issued.
At T+1, 7 x 0.5mg capsules and 14 x 2mg capsules will be issued to allow for a dose increase.
At T+2, 7 capsules of the current dose and 14 capsules of both the lower and higher doses (if applicable) will be issued.
At T+3, 7 capsules of the current dose and 14 capsules of both the lower and higher doses (if applicable) will be issued.
At T+4, 49 capsules of the current dose, and 56 capsules of both the lower and higher doses (if applicable) will be issued.
At the T+5 telephone call an unscheduled visit can be arranged to increase or reduce the dose, therefore 49 capsules of the lower and/or higher dose as applicable will be issued for the remainder of the study.
At the T+6 telephone call an unscheduled visit can be arranged to increase or reduce the dose, therefore 42 capsules of the lower and/or higher dose will be issued as applicable for the remainder of the study.

MENDS Treatment Accountability Log
Version 2.1 031207

Centre Number: _ _ _
Registration Number _ _ _ _ _ _

Unscheduled visits (T+7W to T+12W) for dose reductions only

Visit	Strength	0.5mg	2 mg	6 mg	12 mg	Current Dose	Pharmacy Signature	Date dd/mm/yyyy	RP Signature	Date dd/mm/yyyy
	Quantity of capsules issued									
	Quantity of capsules returned									
	Quantity of capsules issued									
	Quantity of capsules returned									
	Quantity of capsules issued									
	Quantity of capsules returned									
	Quantity of capsules issued									
	Quantity of capsules returned									
	Quantity of capsules issued									
	Quantity of capsules returned									
	Quantity of capsules issued									
	Quantity of capsules returned									
T+12	Quantity of capsules issued									
	Quantity of capsules returned									

At T+12 all packaging and unused medication will be returned to pharmacy.

Packaging and medication returned to PENN for destruction

	0.5mg	2 mg	6 mg	12 mg	Pharmacy Signature	Date dd/mm/yyyy
Quantity of capsules returned to PENN						

Appendix J: SCQ Result Letter

(To be presented on local headed paper)

Centre Name and Number (if applicable): xxx

SCQ Results Letter Version 1.0 Date 26/04/07

MENDS: The use of MElatonin in children with Neuro-developmental Disorders and impaired Sleep; a randomised, double-blind, placebo-controlled, parallel study

ISRCTN05534585

Dear Dr _____,

One of the screeners we used in the MENDS study was the social communication questionnaire. As you know the risk of an autistic spectrum disorder increases with degree of learning disability, such that around one third of children with severe learning difficulties are felt to have autism or an autistic spectrum disorder.

The SCQ is a relatively good screener, but only indicates the risk of a child having autism, not whether or not they have the diagnosis. Published literature suggests autism is more likely with scores above 22 and the broader group of autistic spectrum disorders more likely with scores between 15 and 22.

Child _____ in the MENDS study scored __ on this screener.

Whilst again emphasising that this is not a diagnostic tool this information may be of use to you now or in the future in your management of _____.

If you have any concerns or questions regarding this please contact the responsible doctor:

Dr _____ at _____(Hospital)

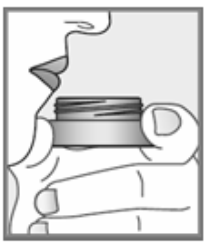
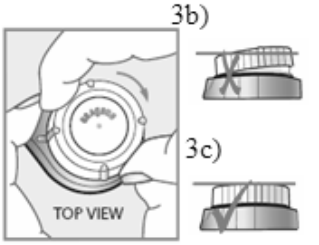
Tel: _____

Yours sincerely,

<<Name>>
<<Position>>

Appendix K: Instructions for Collection of DNA Samples

Oragene®•DNA Collection Kit User Instructions (OG-250 Disc Format)

1) 	2) 	3a) 3b) 	4) 
Please ensure that the child has not eaten, drank, or chewed gum for 30 minutes before taking the saliva sample.			
1 Ask the child to spit saliva into the empty container (Picture #1)	2 They need to spit until the amount of liquid saliva (not bubbles) reaches the level shown in Picture #2	3 Put the container on a flat surface. Screw the cap onto the container. Make sure that the cap is closed tightly, as shown in picture #3c. If you have trouble closing the cap all the way, turn the cap slightly counter-clockwise then try to close it again.	4 Mix gently for at least 10 seconds. Recycle outer packaging.

Tips:

- Do NOT remove plastic film from the lid.
- On average, it takes approximately 2 to 5 minutes to provide a saliva sample.
- Some people may find it hard to spit the recommended amount of saliva. Encourage the child to make more saliva, by asking them to close their mouth and wiggle their tongue or rub their cheeks. If the child is unable to produce a sufficient quantity of saliva by spitting, please use the saliva sponges to obtain the sample (see additional instruction sheet)
- Ensure the child has finished spitting within 30 minutes and immediately close the container.

Intended Use: This product is designed for the safe collection of DNA samples from human saliva.

Contents: The white lid contains 2 mL of Oragene•DNA liquid. Before use, the solution in the lid should be clear and colorless.

Warnings: Do not let the child ingest the Oragene•DNA liquid. Wash with water if the Oragene•DNA liquid comes in contact with eyes or skin.

Storage: Store at room temperature 15-30˚C (59-86˚F).

Using Saliva Sponges to Collect DNA Samples from Infants & Young Children

When using sponges to collect DNA please use the following instructions and disregard the instructions in the container packaging.

Introduction

Saliva can be collected from most adult donors and children by following the user instructions for spitting into the Oragene™ DNA Self-Collection Kit. However, infants and young children are unable to spit the required 1-2 mL of saliva. DNA Genotek has developed a collection procedure for infants and young children that uses saliva sponges and the Oragene DNA Self-Collection kit to collect a sample. DNA yield is proportional to saliva volume. The saliva sponges included in the kit are ideal for collecting the relatively large amount of saliva present in the cheek pouches of young children. More DNA can be collected by taking several saliva sponge samples from each child over a period of time.

Preparing for Saliva Collection

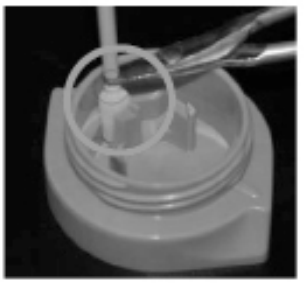
- Caution should always be used when inserting anything into a child's mouth. Do not leave the child unattended when using the sponges. We recommend that you only use the sponges provided and that you do not substitute with other sponges or swabs.
- Although not required, the child may drink water or brush teeth with water before the collection. After rinsing or brushing, wait 10 minutes before collecting a saliva sample. If the child is nursing, wait 15-20 min after feeding before collecting a saliva sample.
- Some children find that the saliva sponge tickles their gums. Depending on the age of the child, it may be helpful to explain ahead of time that the collection will be a fun experience that will not take long and that the sponge may tickle.
- Try not to rub directly on the child's teeth to minimize the amount of bacteria transferred to the sponge.
- If a donor can provide some saliva, but not the full amount, through spitting, it is perfectly acceptable to combine saliva from spitting together with saliva sponges in the same Oragene kit.
- If the donor is unable to provide sufficient saliva within the recommended 10-15 min, the following procedure can be tried. Securely cap the Oragene vial after 15 min – this will release the Oragene fluid. Mix the contents of the vial gently by inversion 5 times. When a second collection is to be attempted (this can be days later if convenient), place the vial on a flat surface and carefully open the vial, taking care to avoid spilling any of the liquid. Place the cap on a flat surface with the inside facing upwards. Proceed with further collection of saliva using the remaining sponges. Extra care should be taken when cutting off the sponge from the handle to avoid spillage. A maximum of 5 sponges should be used per Oragene vial.

Collecting Saliva

1. Place the saliva sponge into the child's mouth in the *cheek pouch* (the space between the gums and the inner cheek). Gently move the saliva sponge around the upper and lower cheek pouches on both sides of the mouth to soak up as much saliva as possible. There is no need to 'scrape' the inner cheek with saliva sponges – simply collect as much saliva as possible from the cheek pouches. The sponge will absorb more saliva if it is left in the child's mouth for a longer time (up to 60 seconds).

2. Once collected, cut the sponge into the blue base of the Oragene kit as follows. Place the sponge firmly against the bottom of the kit between the tooth and the kit wall (see picture below). This action will ensure that the sponge tip remains in the container during the cutting action. Using the scissors provided, cut the narrow part of the handle just above the sponge.

   Recycle/discard the plastic handle. If only one saliva sponge sample is to be collected, proceed to step 4.



3. For the collection of up to 5 saliva sponge samples from the same child, repeat steps 1 and 2. Follow the sequence shown in the diagram below. A rest period of about 5 min between each collection of 2 sponges is helpful. To prevent the saliva samples from drying out, cap the vial (see step 4) within 15 min of the first collection. If you have not had a chance to collect all 5 sponges within 15 minutes, you may carefully re-open the kit. If you remove the cap be sure that the inside is facing upwards when putting it on any surface. Do not spill the contents.

   Follow these steps for collecting multiple sponges:

4. Carefully cap the kit and tighten it firmly. Once the Oragene liquid is released from the cap, it will preserve the DNA collected by the sponge(s).

5. Invert gently 5 times to mix the sample.

6. If the scissors are to be re-used, they should be rinsed with tap water and wiped dry between donors.