CLINICAL TRIAL PROTOCOL

PROTOCOL TITLE:
Improving sleep of children with neurodevelopmental disorders: A Prospective Randomised Controlled Trial using Transcranial Pulsed Current Stimulation versus Melatonin

PROTOCOL VERSION: 4
PROTOCOL DATE: 05/12/2023

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PROTOCOL SIGNATURE PAGE

Protocol Title:
Improving sleep of children with neurodevelopmental disorders: A Prospective Randomised Controlled Trial using Transcranial Pulsed Current Stimulation versus Melatonin

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Protocol Date: 5/12/2023

Industrial Partner: Ascenzion

Declaration of Investigator

I confirm that I have read the above-mentioned protocol and its attachments. I agree to conduct the described trial in compliance with all stipulations of the protocol, regulations and ICH E6 Guideline for Good Clinical Practice (GCP).

Principal Investigator Name: _____NG ZHI MIN _____

Principal Investigator Signature: _____

Date: _____

1 BACKGROUND AND RATIONALE

Children with neurodevelopmental disorders such as cerebral palsy (CP) and autistic spectrum disorder (ASD) are found to have poor sleep.[i,ii,iii,iv] Poor sleep in children with these long-term neurodevelopmental conditions may lead to worsening spasticity, increased caregiver burden and poorer quality of life.[v,vi]

Use of Melatonin and other pharmacological sleep aids, treatment of obstructive sleep apnoea and application of sleep systems are some of the conventional ways to treat sleep problems in these children. In recent years, non-invasive brain stimulation such as transcranial electrical stimulation (TES) has emerged as a potential modality treatment to improve sleep in adult patients with major depressive disorders, bipolar disorders, migraine and Parkinson's disease.[vii,viii,ix,x] TES involves the application of mild electrical current by placing electrodes on the scalp, resulting in the modulation of membrane potentials of the neurons in the underlying brain cortex.[xi] TES of frontal brain regions where sleep slow oscillations originate, has been found to enhance spontaneous slow oscillatory EEG activity which induces sleepiness, ameliorating sleep quality and extending sleep duration.[xii,xiii,xiv] TES may be delivered in the form of transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS) or transcranial pulsed current stimulation (tPCS). tPCS has increasingly gained attention as a novel safe and cost-effective treatment modality for spasticity in children with CP and for improvement of gait in adults with Parkinson's Disease.[xv,xvi] This mode of therapy could serve as a potential alternative for pharmacotherapy in treatment of insomnia in children with neurodevelopmental disorders.[xvii,xviii] However, most studies on sleep intervention used subjective sleep questionnaires and the use of any form of TES to improve sleep has not been studied in children. Thus, we aim to objectively evaluate whether tPCS can improve sleep in children with neurodevelopmental disorders, as compared to Melatonin.

1.1 General Introduction

tPCS is a form of TES that delivers unidirectional pulsed currents at a predetermined frequency to the brain cortex, as opposed to the direct current provided by tDCS. (refer Figure A device) It has been demonstrated that tPCS increases endogenously generated brain oscillations in a frequency-specific manner and facilitates interhemispheric connectivity.[xix,xx,xxi,xxii] In recent studies, tPCS has shown to improve spasticity in children with CP and improve gait and balance in adults with Parkinson's Disease.[xv,xvii] It has been postulated that tPCS may also be used to treat sleep difficulties by modulating dysfunctional inter-hemispheric coordination within the brain's default mode network and visual pathway, thought to be the core predisposing factors in the aetiology of primary insomnia.[xxiii]

1.2 Rationale and Justification for the Study

Sleep disturbance is a common problem in children with neurodevelopmental disorder. Poor sleep leads to worsening spasticity and behaviour and can also affect learning and daytime engagement in school and with family members. Many families seek effective and safe interventions to improve sleep of their children with neurodevelopmental disorder. Use of Melatonin is a safe treatment option but some children may require more sedating pharmacological options to sleep and these medications are not without side effects if on long-term use. A safe and non-invasive intervention that can improve sleep in children with neurodevelopmental disorder is needed.

1.2.1 Rationale for the Study Purpose

Considering the clinical need to improve sleep in children with neurodevelopmental disorder and the high safety profile of non-invasive TES in children[xxiv,xxv,xxvi] and the potential benefit of high frequency transcranial pulsed current stimulation applied at the cerebellum to modulate sleep-cycles, we aim to study the effectiveness in improving sleep in children with neurodevelopmental disorder.

1.2.2 Rationale for Doses Selected

tPCS has been shown to reach subcortical brain targets like the hippocampus from surface application on the cortex, to the extent that the hippocampus is associated with deep sleep and is sensitive to **400Hz** current stimulation in the inducement of LTP, there is a possibility that **400Hz** tPCS may modulate sleep stages via influencing plasticity of the hippocampal formation.[xxvii,xxviii]

The **cerebellum** displays various sorts of rhythmic activities that covers high-frequency oscillations, thus artificial resonance similar to intrinstic rhythms (400hz is within the high frequency category) may entrain intrinsic oscillations of the cerebellum based on resonance theory.[xxix,xxx,xxxi,xxxii] Preliminary studies have shown that the tDCS in the **prefronto-cerebellar area** improves sleep quality in euthymic bipolar patients.[x] The human **cerebellum** is easily accessible to non-invasive stimulation such as TES due to its anatomical location, and less painful compared to stimulating the prefrontal brain regions , making it more tolerable in children.[xxxiii]

The low intensity current delivered by tPCS is between **1mA** to 2mA, about 800-1000 times weaker than conventional electroconvulsive therapy used in treating neuropsychiatry diseases. The working mechanism of tPCS has been suggested to involve the induction of static and dynamic current components to modulate transmembrane neuronal potentials, which can influence the "excitability-inhibitory balance" of cortical brain areas and regulate homeostasis in complex internal systems.[xix]

Based on safety recommendations of TES in children, current intensities of **~1mA** are often used, but trials up to 2 mA without serious adverse effects have been reported.[xxxiv]

High frequency **400Hz, cerebello-cerebral** tPCS at **1mA**, **30mins per day over 12 weeks**, has been tested in a study on 63 children with Cerebral Palsy, age 2 to 12 years old, to improve gross motor functions and spasticity, with no adverse event reported.[xv]

1.2.3 Rationale for Study Population

Preliminary studies have shown that tPCS was effective in improving spasticity in children with cerebral palsy while tDCS was effective in improving behaviour in children with ASD.[xv,xxxv,xxxvi] This study will focus on effectiveness in sleep in this group of population.

1.2.4 Rationale for Study Design

The unique Two-Period, Four-Sequence (Balaam's) design is used in this crossover trial in which each subject serves as his or her own control. Therefore the estimated treatment differences tend to have less variability than that observed in a parallel design. Smaller variability leads to a smaller sample size. Also, the repeated- measurements feature of a crossover design eliminates the need for a lengthy run-in or baseline period. Moreover, Balaam's design is a hybrid of a crossover design and a parallel design, whereby the estimated treatment difference is unbiased even in the presence of unequal carryover

effects.[xxxvii]

HYPOTHESIS AND OBJECTIVES

1.3 Hypothesis

tPCS is effective in improving total sleep time in children with neurodevelopmental disorder.

1.4 Primary Objectives

The primary objective is to assess the effectiveness of tPCS in improving total sleep time by 20% in children with neurodevelopmental disorder, compared with using Melatonin.

1.5 Secondary Objectives

The secondary objective is to evaluate improvement in other objective sleep measures such as sleep onset latency, sleep efficiency, and wake after sleep onset based on actigraphy; and subjective sleep measures such as sleep initiation, sleep maintenance, sleep quality and change in behaviour based on questionnaires in children with neurodevelopmental disorder.

We also hypothesise that objective improvement in sleep quality will correlate with a decreased score in Sleep Disturbance Scale in Children questionnaire.

1.6 Potential Risks and Benefits:

1.6.1 Potential Risks

tPCS may cause discomfort or tingling sensation to some people. Some people may have skin redness due to allergic reaction to electrode. Few people may complain of headache post stimulation. Otherwise, there is minimal risk in tPCS if there are no contraindication.

1.6.2 Potential Benefits

Use of tPCS is potentially an effective intervention for children with neurodevelopmental disorder that can improve spasticity, motor function and sleep.

2 STUDY POPULATION

2.1 List Number and Nature of Subjects to be enrolled

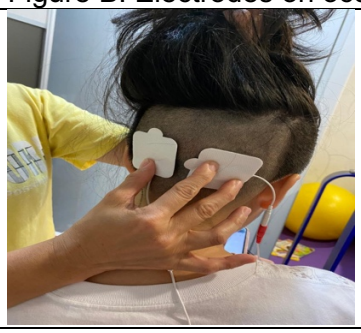
Based on a two-sided paired t-test at 80% power and 5% one-sided alpha with 20% drop-out rate, a sample size of 40 is required to detect 20% improvement in primary end-point (total sleep time), assuming 15% standard deviation.

2.2 Criteria for Recruitment and Recruitment Process

The eligible participants will be recruited from the families who receive services and/or medical follow-up at KKH. Information of the study and Consent Form will be provided to the families who show interest in the study.

2.3 Inclusion Criteria

- Aged 4-16
- Neurodevelopmental disorder including cerebral palsy, autistic spectrum disorder, neurogenetic syndrome.
- Patients whose pre-intervention sleep questionnaire total score more than 46 and/or pre-intervention sleep questionnaire T-score more than 70 in any sleep domain
- Children agree to tPCS as per procedure and consent to the study, including need to shave hair at the site of stimulation at the occiput (refer Figure B)
- Parents/carers agree to bring children to KKH for tPCS as per visit schedule and procedure
- Medical practitioner's approval

Figure A: tPCS device	Figure B: Electrodes on occiput
	

2.4 On Exclusion Criteria

History of uncontrolled epileptic disorders and seizures, brain tumours or trauma and mental diseases, substance abuse or dependence, use of benzodiazepines, neuroleptic, serotonin or dopaminergic drugs, presence of metal/ electronic implant in brain/ body eg. shunt, cochlear implant, pacemaker or defibrillator, known untreated obstructive sleep apnoea or other sleep disorder, and current involvement in other tDCS or rTMS trials. Patients with history of drug allergy to Melatonin will also be excluded.

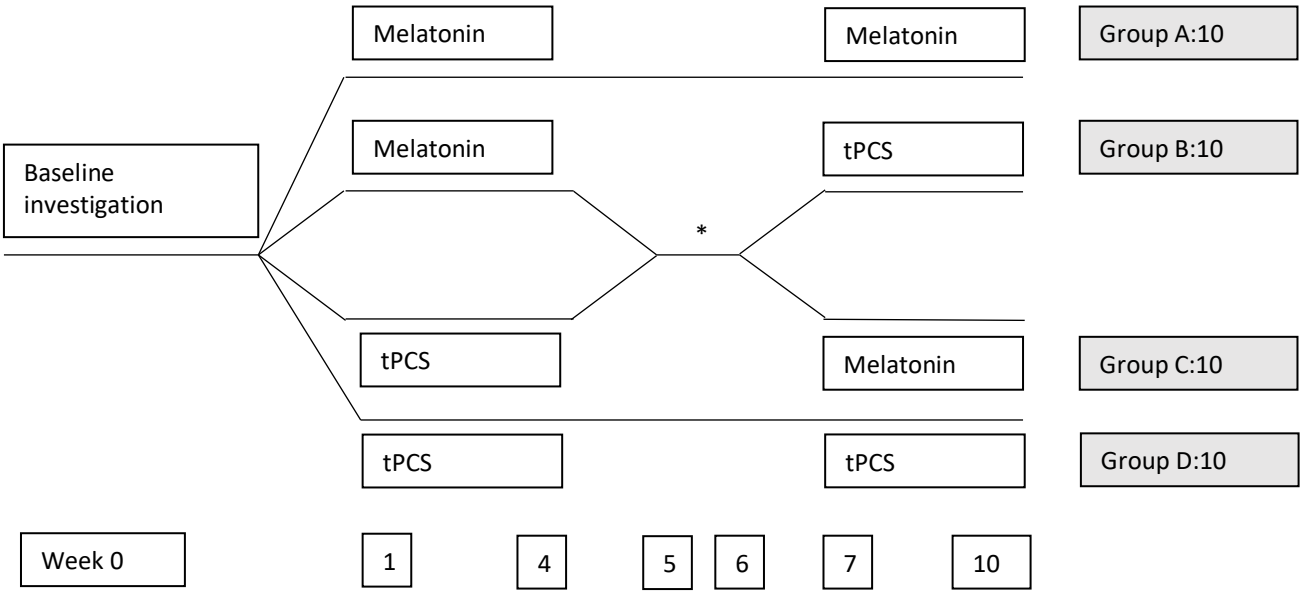
2.5 Subject Replacement

Drop-out definition: Any participant who reports significant adverse effects, are unable tolerate the session, or withdraw from the study will be considered drop-out.

Subjects who drop out will not be replaced.

3 STUDY DESIGN

Figure C: Study Design



At baseline (week 0), all patients will do a one-week sleep actigraphy and complete SDSC questionnaire. At week 1, patients will be randomised to one of the 4 treatment regimen that is determined by the first period of the sequence they are assigned to. Re-evaluation with sleep actigraphy and SDSC questionnaire will be done at week 4, 6 and 10. At week 7, the patients will cross over to the treatment for the second period of the sequence they are assigned to. Over the 10-week period, sleep diary will also be completed daily.

10 patients will receive dose-appropriate Melatonin over 8 weeks (Group A), 10 patients will receive 40 sessions of home-based tPCS over 8 weeks (Group D), 10 patients will receive 4 weeks of Melatonin then cross over to receive 4 weeks of 20 sessions of home-based tPCS (Group B) and 10 patients will receive 4 weeks of 20 sessions of home-based tPCS then cross over to receive Melatonin over 4 weeks (Group C).

There will be a washout period of 2 weeks (week 5 and 6) between cross over. Those on a Melatonin group cross over will also go through the same washout period.

3.1 Randomisation and Blinding

Randomisation will be conducted for the patients in a 1:1 ratio to two treatment groups in two sequence periods.

Randomisation will be carried out by one study team member uninvolved in the final data analysis. The study member reporting the actigraphy, and the study member performing data analysis will be blinded.

3.2 Contraception and Pregnancy Testing

Not applicable.

3.3 Study Visits and Procedures

Visit to KKH	**Visit 1**		**Visit 2**	**Visit 3**		**Visit 4**
Timeline	**Week 0**	**Week 1-4**	**Week 4**	**Week 6**	**Week 7-10**	**Week 10**
Procedure	**Baseline assessment**	**First sequence Intervention Period**	**Post-first sequence assessment**	**Pre-second sequence assessment**	**Second sequence Intervention Period**	**Post-second sequence assessment**
Informed Consent[1]	X					
Questionnaires[2]	X		X	X		X
Actigraphy[3]	X		X	X		X
tPCS[4] or Melatonin[5]		X			X	

[1]Informed Consent will be taken at screening visit, i.e. on the same day as when they are identified as a potential participant. Randomisation will be performed after consent taking is completed.
[2]Sleep questionnaires
2.1 Sleep disturbance scale for children (SDSC) and Aberrant Behavior Checklist (ABC)
2.2 WHO International Classification of Functioning, Disability and Health, Children & Youth version (ICF-CY) sleep ratings
[3]Actigraphy. Participants will collect the Actiwatch and wear it for 1 week at home for whole night actigraphic data at start of the sequence period (Week 0 and Week 6) and at the end of the sequence period (Week 4 and Week 10). Patients will return the Actiwatch at the end of the study.
[4]Transcranial Pulsed Current Stimulation (tPCS) – for intervention arm. 45min/ session of tPCS will be performed at home, supervised by a trained personnel, Monday to Friday for 20 sessions over 4 weeks in each sequence period. Participants will be asked to fill out the compliance/ adverse event log daily.
[5]In the control group, participants will be given Melatonin over 4 weeks in each sequence period. They will be asked to fill out the compliance/ adverse event log daily.

3.3.1 Screening Visits and Procedures

All KKH patients who are attending outpatient clinics for neurology service and/ or Physiotherapy and will be screened accordingly to the inclusion and exclusion criteria as stated in the preceding sections 3.2 to 3.4 by the doctors in the clinic. Consent will be taken by anyone from the study team.

3.3.2 Study Visits and Procedures

Baseline
Prior to commencement of intervention, the patient will undergo:

I. Actigraphy

Actigraphy is a method used to study sleep-wake patterns and circadian rhythms by assessing movement, most commonly of the wrist.[xxxviii] We will be collecting whole night actigraphic data using Actiwatch (Actiwatch 2, Respironics, USA), worn on the nondominant wrist or ankle – 7 days before intervention commences and in the last week of intervention/control. The four sleep statistics include total sleep time [TST (min)], sleep onset latency [SOL or period of time between bedtime and sleep start (min)], sleep efficiency [percentage of time in bed actually spent sleeping (%)], and wake after sleep onset (WASO) [the time in a sleep interval scored as wake (min)].

II. Sleep disturbance scale for children (SDSC) questionnaire

The SDSC is a 26-item questionnaire that evaluates sleep disturbances including sleep CR initiation/maintenance, breathing, arousal, transitions, daytime sleepiness and sweating in children. [xxxix]

III. Aberrant Behaviour Checklist (ABC)

The ABC is a behavior rating scale for the assessment of treatment effect. It consists of five factors including (i) Irritability, Agitation, Crying; (ii) Lethargy, Social withdrawal; (iii) Stereotypic behaviour; (iv) Hyperactivity, Non-compliance; and (v) Inappropriate Speech. This will only be used for participants with autistic spectrum disorder.

IV. ICF-CY sleep ratings

Using the WHO International Classification of Functioning, Disability and Health, Children & Youth version (ICF-CY) in the domain of Body Structure/ Function, sleep is evaluated in four aspects: amount of sleep (B1340), onset of sleep (B1341), maintenance of sleep (B1342) and quality of sleep (B1343).[17] Levels of ICF-CY impairment was graded according to frequency, intrusiveness or severity: from 0 (no impairment/ difficulty) to 4 (complete/ constant impairment/ difficulty/ intensity totally disruptive).[18]

V. EQ5D

Quality of life measures will be collected and compared between groups.

Intervention

Throughout the intervention period of 6 weeks, patients from the intervention arm will be receiving tPCS, 0.7-1mA for 45 min/ day Monday to Friday (non-public holiday) over 4 weeks in each sequence period. Any adverse event will be recorded in the adverse event log.

Post-intervention

Intervention group: Participants will wear the Actiwatch for 7 nights-actigraphic data in the last week of sequence period. Sleep questionnaires will be completed on the last day of the sequence period.

Control group: Participants will take Melatonin daily at bedtime for 4 weeks and wear the Actiwatch for 7 nights-actigraphic data in the last week of each sequence period. Sleep questionnaires will be completed on the last day of the sequence period.

3.4 Discontinuation/Withdrawal

3.4.1 Discontinuation Criteria

Study intervention will be discontinued if subject is unable to tolerate the tPCS or Melatonin.

3.4.2 Discontinuation Visit and Procedures

Subjects may withdraw voluntarily from participation in the study at any time. If withdrawal occurs, subjects will still be asked to complete a questionnaire to study the reason for withdrawal. Actigraphy will be done (if any) to the point of withdrawal from participation in the study.

4 TRIAL MATERIALS

4.1 Trial Product (s)

HSA CRM notification
The tPCS is an electrical and neuromuscular stimulator classified as a general medical device. Clinical Research Material Notification from Health Science Authority Singapore has been obtained.

Refer Annex B for picture of device.
Technical Information of the tPCS (AscenZ-IV Multi-channel Pulsed Current Stimulator; Yiqi Biotechnology Co. Ltd., China):

- Intensity: 0.7-1mA
- Waveform: Monophasic square wave
- Pulse width: 140μs
- Frequency: 400Hz
- Electrode materials: self-adhesive silica gel patch
- Electrode size: 5*5cm

5 TREATMENT

5.1 Rationale for Selection of Dose of Intervention

1) Based on safety recommendations of TES in children, reduced (~1 mA) current intensities are often used, but trials up to 2 mA without serious adverse effects are reported [42].
2) A study period of 20 sessions of 45 minutes duration is based on manufacturer's clinical experience, unpublished data.

5.2 Intervention settings

The intervention is the tPCS and it will be administered by trained personnel of the industrial partner. .

5.3 Intervention Administration

45min/ session of tPCS will be performed at home, supervised by a trained personnel, Monday to Friday for 20 sessions over 4 weeks in each sequence period.

5.4 Specific Restrictions / Requirements

Nil as long as exclusion criteria is not met.

5.5 Blinding

Blinding is not done to the patients. Only the study member reporting the actigraphy, and the study member performing data analysis will be blinded.

5.6 Concomitant therapy

Subjects can continue regular standard care.

6 SAFETY MEASUREMENTS

6.1 Definitions

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity, or
- is a congenital anomaly/birth defect

6.2 Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to CIRB

Only related SAEs (definitely/ probably/ possibly) will be reported to CIRB. Related means there is a reasonable possibility that the event may have been caused by participation in the clinical trial. Please refer to the CIRB website for more information on Reporting Requirement and Timeline for Serious Adverse Events.

The investigator is responsible for informing CIRB after first knowledge that the case qualifies for reporting. Follow-up information will be actively sought and submitted as it becomes available.

Related AEs will not be reported to CIRB. However, the investigator is responsible to keep record of such AEs cases at the Study Site File.

6.3 Collecting, Recording and Reporting of Serious Adverse Events (SAEs) to the Health Science Authority (HSA)

All SAEs that are unexpected and related to the study drug will be reported to HSA. Please refer to the HSA website for more information on Safety Reporting Requirements for Clinical Trials.

6.4 Safety Monitoring Plan

All data will be entered into a secure password-protected document in the desktop. Access to the data will only be open to the study investigators. Hardcopy of the data forms will be stored in a locked cupboard in the department.

All adverse events of tPCS in all participants will also be logged and safety of tPCS will be monitored by the principal investigator.

6.5 Complaint Handling

If there is any complaint of the tPCS, the Principal Investigator will be informed immediately to rectify the issue. If the subject is unable to tolerate the tPCS, the study will be discontinued.

7 DATA ANALYSIS

7.1 Data Quality Assurance

The Principal Investigator will ensure accuracy of the data entered. Identifiable patient data will be anonymised. Access to the data will only be open to the investigators in the team.

7.2 Data Entry and Storage

All data will be entered into a secure password-protected document in the desktop. Access to the data will only be open to the study investigators. The Principal Investigator will ensure accuracy of the data entered. Hardcopy of the data forms will be stored in a locked cupboard in the department.

8 SAMPLE SIZE AND STATISTICAL METHODS

8.1 Determination of Sample Size

In an inequality test on data from the Balaam's crossover design, a sample size of 32 achieves 83% power at a 5% significance level when the absolute difference between the two treatment means is 0.2 and the within-subject standard deviation is 0.15. To account for 20% drop-out rate, a sample size of 40 (10 in each arm) is required.

8.2 Statistical and Analytical Plans

The SPSS® 25.0 software (IBM, Armonk, New York, United States) will be used, with statistical significance defined as a p-value of <0.05. Independent t-tests will be conducted to compare differences in outcomes between the two treatment groups; Wilcoxon signed-rank test will be used to compare continuous variables at start and end of treatment. Average of actigraphic measurements were used to compare effects of treatment on sleep parameters. One-way Repeated Measure ANOVA will be conducted to assess changes in outcomes and patient scores within the group across the timepoints. Non-parametric testing will also be conducted to observe for significant differences in patient outcomes within the groups at each timepoint.

9 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

The investigator(s)/institution(s) will permit study-related monitoring, audits and/or IRB review and regulatory inspection(s), providing direct access to source data/document.

10 QUALITY CONTROL AND QUALITY ASSURANCE

The principal investigator will ensure adherence with the protocol and accuracy in relation to data entry. Quality of the data will be ensured and monitored every month during the study period.

The investigator will maintain essential study documents (protocol and amendments, source documentation, relevant correspondence, and all other supporting documentation) in a confidential manner as required by the approving ethics committee.

11 ETHICAL CONSIDERATIONS

This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with the Good Clinical Practice and the applicable regulatory requirements.

This final Clinical Trial Protocol, including the final version of the Participant Information Sheet and Consent Form, must be approved in writing by the Centralised Institutional Review Board (CIRB) and regulatory approval from Health Sciences Authority (HSA), prior to enrolment of any patient into the study.

The principal investigator is responsible for informing the CIRB and HSA of any amendments to the protocol or other study-related documents, as per local requirement.

11.1 Informed Consent

In obtaining and documenting informed consent, the investigator will comply with the GCP guidelines and to the ethical principles that have their origin in the Declaration of Helsinki. Potential participant will be identified by therapist or doctor in KKH/and if inclusion criteria met, consent will be signed in the presence of a witness. Consent taking will take place in the clinic room or rehab outpatient room. The study investigator will sign the consent and make sure that study information is correctly given to the study participant.

If the child has some but not full understanding of the Participant Information Sheet & Consent Form (attached to Section P6), (aged 6 and above), the simplified version (i.e. Child/ Participant Assent Form) will be used. If the child aged 13 and above, has sufficient understanding of the Participant Information Sheet & Consent Form, he will sign it with the parent co-signing in the legal guardian section.

11.2 Confidentiality of Data and Patient Records

All data will be entered into a secure password-protected document in the desktop. Identifiable patient data will be anonymised. Access to the data will only be open to the study investigators. Hardcopy of the data forms will be stored in a locked cupboard in the department.

12 PUBLICATIONS

Following approval by CIRB, the study will be registered on ClinicalTrials.Gov by the Principal Investigator. Study results will be published in peer-reviewed scientific literature regardless of the trial's

outcome. The CONSORT 2010 Statement will be adhered to in publication of study findings to ensure that international standards of authorship and publication are met.

13 RETENTION OF TRIAL DOCUMENTS

When the study is completed, the research data will be kept in a secure password-protected document in the desktop at the department. All the documents will be retained for at least 7 years after completion of the research study.

14 FUNDING and INSURANCE

FUNDING AND RESOURCES

In cash:

Item	Total
Actigraphy ($2600 x 2)	$5,600
Travel allowance 40 subjects x $50	$2,000
Melatonin ($25 for 70s) x 72 bottles	$1,800
Research Coordinator (0.1 FTE x 2 years)	$12,000
IRB application	$800
Presentation at overseas conference	$3,200
Total	$25,000

In-kind contributions:

KKH will supply the manpower for recruitment of study subjects and carrying out objective assessments and questionnaires for the study subjects.

Ascenzion will supply up to 8 tPCS units and the manpower for carrying out the tPCS for the participants during the study period.

REFERENCES

[i] Marriner A, Pestell C, Bayliss D, McCann M, Bucks R. Confirmatory factor analysis of the Sleep Disturbance Scale for Children (SDSC) in a clinical sample of children and adoles- cents. J Sleep Res 2017;26:587-94.

[ii] Romeo DM, Brogna C, Musto E, et al. Sleep disturbances in preschool age children with cerebral palsy: a questionnaire study. Sleep Med 2014;15:1089-93.

[iii] Newman C, O'Regan M, Hensey O. Sleep disorders in children with cerebral palsy. Dev Med Child Neurol. 2006; 48:564–8. [PubMed: 16780625]

[iv] ZM Ng. JB Lin, PC Khoo, VS Rajadurai, DWS Chan, HT Ong, J Wong, CT Choong, KW Lim, KBL Lim, TH Yeo. Causes, functional outcomes and healthcare utilisation of people with cerebral palsy in Singapore. Ann Acad Med Singap 2021;50:111-8

[v] Mol EM, Monbaliu E, Ven M, Vergote M, Prinzie P. The use of night orthoses in cerebral palsy treatment: sleep disturbance in children and parental burden or not? Res Dev Disabil 2012; 33:341-9.

[vi] Sleep Med. 2011 March ; 12(3): 252–256. doi:10.1016/j.sleep.2010.07.019.

[vii] Zhou Q, Yu C, Yu H, Zhang Y, Liu Z, Hu Z, Yuan TF, Zhou D. The effects of repeated transcranial direct current stimulation on sleep quality and depression symptoms in patients with major depression and insomnia. Sleep Med. 2020 Jun;70:17-26. doi: 10.1016/j.sleep.2020.02.003. Epub 2020 Feb 20. PMID: 32179428.

[viii] Kosari, Z., Dadashi, M., Maghbouli, M., & Mostafavi, H. Comparing the Effectiveness of Neurofeedback and Transcranial Direct Current Stimulation on Sleep Quality of Patients With Migraine. *Basic and Clinical Neuroscience, 10*(6), 579-588. https://doi.org/10.32598/BCN.10.6.651.3

[ix] Hadoush H, Al-Sharman A, Khalil H, Banihani SA, Al-Jarrah M. Sleep Quality, Depression, and Quality of Life After Bilateral Anodal Transcranial Direct Current Stimulation in Patients with Parkinson's Disease. Med Sci Monit Basic Res. 2018 Nov 19;24:198-205. doi: 10.12659/MSMBR.911411. PMID: 30449881; PMCID: PMC6259567.

[x] Minichino A, Bersani FS, Spagnoli F, Corrado A, De Michele F, Calò WK, Primavera M, Yang B, Bernabei L, Macrì F, Vergnani L, Biondi M, Delle Chiaie R. Prefronto-cerebellar transcranial direct current stimulation improves sleep quality in euthymic bipolar patients: a brief report. Behav Neurol. 2014;2014:876521. doi: 10.1155/2014/876521. Epub 2014 Dec 7. PMID: 25544804; PMCID: PMC4273569.

[xi] Yavari, F., Jamil, A., Mosayebi Samani, M., Vidor, L.P., Nitsche, M.A., 2018. Basic and functional effects of transcranial electrical stimulation (tES)-an introduction. Neurosci. Biobehav. Rev. 85, 81–92.

[xii] Annarumma L, D'Atri A, Alfonsi V, De Gennaro L. The Efficacy of Transcranial Current Stimulation Techniques to Modulate Resting-State EEG, to Affect Vigilance and to Promote Sleepiness. Brain Sci. 2018 Jul 20;8(7):137. doi: 10.3390/brainsci8070137. PMID: 30037023; PMCID: PMC6071002.

[xiii] Grimaldi D, Papalambros NA, Zee PC, Malkani RG. Neurostimulation techniques to enhance sleep and improve cognition in aging. Neurobiol Dis. 2020 Jul;141:104865. doi: 10.1016/j.nbd.2020.104865. Epub 2020 Apr 4. PMID: 32251840.

[xiv] Hathaway E, Morgan K, Carson M, Shusterman R, Fernandez-Corazza M, Luu P, Tucker DM. Transcranial Electrical Stimulation targeting limbic cortex increases the duration of human deep sleep. Sleep Med. 2021 Mar 8;81:350-357. doi: 10.1016/j.sleep.2021.03.001. Epub ahead of print. PMID: 33812203.

[xv] Liu Z, Dong S, Zhong S, Huang F, Zhang C, Zhou Y, Deng H. The effect of combined transcranial pulsed current stimulation and transcutaneous electrical nerve stimulation on lower limb spasticity in children with spastic cerebral palsy: a randomized and controlled clinical study. BMC Pediatr. 2021 Mar 24;21(1):141. doi: 10.1186/s12887-021-02615-1. PMID: 33761932; PMCID: PMC7989146.

[xvi] Alon G, Yungher DA, Shulman LM, Rogers MW. Safety and immediate effect of noninvasive transcranial pulsed current stimulation on gait and balance in Parkinson disease. Neurorehabil Neural Repair. 2012;26(9):1089–95. https://doi.org/10.1177/1545968312448233.

[xvii] Rosa MA, Lisanby SH. Somatic treatments for mood disorders. Neuro- psychopharmacology 2012;37(1):102.

[xviii] Viganò, A., D'Elia, T. S., Sava, S. L., Auvé, M., De Pasqua, V., Colosimo, A., et al., (2013). Transcranial Direct Current Stimulation (tDCS) of the visual cortex: A proof-of-concept study based on interictal electrophysiological abnormalities in migraine. *The Journal of Headache and Pain, 14*(1), 23.

[xix] Jaberzadeh S, Bastani A, Zoghi M, Morgan P, Fitzgerald PB. Anodal transcranial pulsed current stimulation: the effects of pulse duration on corticospinal excitability. PLoS One. 2015;10(7):e0131779. https://doi.org/10.1371/journal.pone.0131779.

[xx] Castillo Saavedra L, Morales-Quezada L, Doruk D, Rozinsky J, Coutinho L, Faria P, et al. QEEG indexed frontal connectivity effects of transcranial pulsed current stimulation (tPCS): a sham-controlled mechanistic trial. Neurosci Lett. 2014;577:61–5. https://doi.org/10.1016/j.neulet.2014.06.021.

[xxi] Morales-Quezada L, Leite J, Carvalho S, Castillo-Saavedra L, Cosmo C, Fregni F. Behavioral effects of transcranial pulsed current stimulation (tPCS): speed accuracy tradeoff in attention switching task. Neurosci Res. 2016;109:48–53.

https://doi.org/10.1016/j.neures.2016.01.009.
[xxii] Ma Z, Du X, Wang F, Ding R, Li Y, Liu A, et al. Cortical plasticity induced by anodal transcranial pulsed current stimulation investigated by combining two-photon imaging and electrophysiological recording. Front Cell Neurosci. 2019;13:400. https://doi.org/10.3389/fncel.2019.00400.
[xxiii] Dai XJ, Liu BX, Ai S, Nie X, Xu Q, Hu J, Zhang Q, Xu Y, Zhang Z, Lu G. Altered inter-hemispheric communication of default-mode and visual networks underlie etiology of primary insomnia: Altered inter-hemispheric communication underlie etiology of insomnia. Brain Imaging Behav. 2020 Oct;14(5):1430-1444. doi: 10.1007/s11682-019-00064-0. PMID: 31011953.
[xxiv] Antal A, Alekseichuk I, Bikson M, Brockmöller J, Brunoni AR, Chen R, Cohen LG, Dowthwaite G, Ellrich J, Flöel A, Fregni F, George MS, Hamilton R, Haueisen J, Herrmann CS, Hummel FC, Lefaucheur JP, Liebetanz D, Loo CK, McCaig CD, Miniussi C, Miranda PC, Moliadze V, Nitsche MA, Nowak R, Padberg F, Pascual-Leone A, Poppendieck W, Priori A, Rossi S, Rossini PM, Rothwell J, Rueger MA, Ruffini G, Schellhorn K, Siebner HR, Ugawa Y, Wexler A, Ziemann U, Hallett M, Paulus W. Low intensity transcranial electric stimulation: Safety, ethical, legal regulatory and application guidelines. Clin Neurophysiol. 2017 Sep;128(9):1774-1809. doi: 10.1016/j.clinph.2017.06.001. Epub 2017 Jun 19. PMID: 28709880; PMCID: PMC5985830.
[xxv] Zewdie E, Ciechanski P, Kuo HC, Giuffre A, Kahl C, King R, Cole L, Godfrey H, Seeger T, Swansburg R, Damji O, Rajapakse T, Hodge J, Nelson S, Selby B, Gan L, Jadavji Z, Larson JR, MacMaster F, Yang JF, Barlow K, Gorassini M, Brunton K, Kirton A. Safety and tolerability of transcranial magnetic and direct current stimulation in children: Prospective single center evidence from 3.5 million stimulations. Brain Stimul. 2020 May-Jun;13(3):565-575. doi: 10.1016/j.brs.2019.12.025. Epub 2019 Dec 30. PMID: 32289678.
[xxvi] Krishnan C, Santos L, Peterson MD, Ehinger M. Safety of noninvasive brain stimulation in children and adolescents. Brain Stimul. 2015 Jan-Feb;8(1):76-87. doi: 10.1016/j.brs.2014.10.012. Epub 2014 Oct 28. PMID: 25499471; PMCID: PMC4459719.
[xxvii] Datta A, Dmochowski JP, Guleyupoglu B, Bikson M, Fregni F. Cranial electrotherapy stimulation and transcranial pulsed current stimulation: a computer based high-resolution modeling study. Neuroimage. 2013 Jan 15;65:280-7. doi: 10.1016/j.neuroimage.2012.09.062. Epub 2012 Oct 5. PMID: 23041337.
[xxviii] Spanò G, Weber FD, Pizzamiglio G, McCormick C, Miller TD, Rosenthal CR, Edgin JO, Maguire EA. Sleeping with Hippocampal Damage. Curr Biol. 2020 Feb 3;30(3):523-529.e3. doi: 10.1016/j.cub.2019.11.072. Epub 2020 Jan 16. PMID: 31956024; PMCID: PMC6997880.
[xxix] de Solages C, Szapiro G, Brunel N, Hakim V, Isope P, Buisseret P, Rousseau C, Barbour B, Léna C. High-frequency organization and synchrony of activity in the purkinje cell layer of the cerebellum. Neuron. 2008 Jun 12;58(5):775-88. doi: 10.1016/j.neuron.2008.05.008. PMID: 18549788.
[xxx] Servais L, Bearzatto B, Schwaller B, Dumont M, De Saedeleer C, Dan B, Barski JJ, Schiffmann SN, Cheron G. Mono- and dual-frequency fast cerebellar oscillation in mice lacking parvalbumin and/or calbindin D-28k. Eur J Neurosci. 2005 Aug;22(4):861-70. doi: 10.1111/j.1460-9568.2005.04275.x. PMID: 16115209.
[xxxi] Cheron J, Cheron G. Beta-gamma burst stimulations of the inferior olive induce high-frequency oscillations in the deep cerebellar nuclei. Eur J Neurosci. 2018 Oct;48(8):2879-2889. doi: 10.1111/ejn.13873. Epub 2018 Mar 9. PMID: 29460990.
[xxxii] Zaehle T, Rach S, Herrmann CS. Transcranial alternating current stimulation enhances individual alpha activity in human EEG. PLoS One. 2010 Nov 1;5(11):e13766. doi: 10.1371/journal.pone.0013766. PMID: 21072168; PMCID: PMC2967471.
[xxxiii] Grimaldi G, Argyropoulos GP, Bastian A, Cortes M, Davis NJ, Edwards DJ, Ferrucci R, Fregni F, Galea JM, Hamada M, Manto M, Miall RC, Morales-Quezada L, Pope PA, Priori A, Rothwell J, Tomlinson SP, Celnik P. Cerebellar Transcranial Direct Current Stimulation (ctDCS): A Novel Approach to Understanding Cerebellar Function in Health and Disease. Neuroscientist. 2016 Feb;22(1):83-97. doi: 10.1177/1073858414559409. Epub 2014 Nov 18. PMID: 25406224; PMCID: PMC4712385.
[xxxiv] Bikson M, Grossman P, Thomas C, Zannou AL, Jiang J, Adnan T, Mourdoukoutas AP, Kronberg G, Truong D, Boggio P, Brunoni AR, Charvet L, Fregni F, Fritsch B, Gillick B, Hamilton RH, Hampstead BM, Jankord R, Kirton A, Knotkova H, Liebetanz D, Liu A, Loo C, Nitsche MA, Reis J, Richardson JD, Rotenberg A, Turkeltaub PE, Woods AJ. Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016. Brain Stimul. 2016 Sep-Oct;9(5):641-661. doi: 10.1016/j.brs.2016.06.004. Epub 2016 Jun 15. PMID: 27372845; PMCID: PMC5007190.
[xxxv] Hadoush H, Nazzal M, Almasri NA, Khalil H, Alafeef M. Therapeutic Effects of Bilateral Anodal Transcranial Direct Current Stimulation on Prefrontal and Motor Cortical Areas in Children with Autism Spectrum Disorders: A Pilot Study. Autism Res. 2020 May;13(5):828-836. doi: 10.1002/aur.2290. Epub 2020 Mar 9. PMID: 32149480.
[xxxvi] Osório AAC, Brunoni AR. Transcranial direct current stimulation in children with autism spectrum disorder: a systematic scoping review. Dev Med Child Neurol. 2019 Mar;61(3):298-304. doi: 10.1111/dmcn.14104. Epub 2018 Nov 19. PMID: 30451290.

[xxxvii] Craig TJ, Teets S, Lehman EB, Chinchilli VM, Zwillich C. Nasal congestion secondary to allergic rhinitis as a cause of sleep disturbance and daytime fatigue and the response to topical nasal corticosteroids. J Allergy Clin Immunol. 1998 May;101(5):633-7. doi: 10.1016/s0091-6749(98)70171-x. PMID: 9600500.

[xxxviii] Littner M, Kushida CA, Anderson WM, Bailey D, Berry RB, Davila DG, et al. Practice parameters for the role of actigraphy in the study of sleep and circadian rhythms: an update for 2002. Sleep 2003;26:337e41.
[xxxix] Bruni, O., Ottavianio, S., Guidetti, V., Romoli, M., Innocenzi, M., Cortesi, F., & Giannotti, F. (1996). The Sleep Disturbance Scale for Children (SDSC): Construction and validation of an instrument to evaluate sleep disturbances in childhood and adolescence. J. Sleep Rrs, 5, 251-261.