CLINICAL TRIAL PROTOCOL

PROTOCOL TITLE:
Effectiveness in Improving gait and Value of a Transcutaneous Electrical Stimulation garment in children with Cerebral Palsy in Singapore

PROTOCOL NUMBER:
2

PROTOCOL VERSION: 2
PROTOCOL DATE: 30 Mar 2020

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PROTOCOL SIGNATURE PAGE

Protocol Title:
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Protocol Version/ Date: 30/03/2020

Sponsor Name:
Funded by KKH Academic Medicine (AM) Research Start-Up July 2019 Grant Call
Industrial Partner: Inerventions

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

Worldwide, the prevalence of cerebral palsy (CP) is 1.77-2.9 per 1000 live births.[i,ii,iii] CP describes a group of developmental disorders of movement and posture, attributed by a non-progressive interference, lesion, or abnormality in the immature brain, causing activity restriction or disability. CP is a complex condition that is also accompanied by disturbance in sensation, cognition, communication and/or behaviour as well as secondary musculoskeletal problems.[iv]Common musculoskeletal problems in CP include spasticity and weakness which affect gait.

Among the treatment modalities for CP, transcutaneous electrical nerve stimulation (TENS) or neuromuscular electrical stimulation (NMES) is one intervention that has been shown to be effective in muscle tone reduction. A systematic review showed significant evidence, based on 14 randomised controlled trials (RCTs) with 550 study participants evaluating the effect of TENS, for management of limb spasticity.[v] Another review of electrical stimulation for children with CP showed that use of NMES offered benefits such as increased muscle strength, range of motion and function in children with CP.[vi] In combination with dynamic splinting, NMES was more effective than either treatment on its own in improving function and posture. Two out of six TENS studies in a systematic review evaluating efficacy of electrical stimulation in improving motor function of children in CP reported statistically significant improvements, two studies reported no statistically significant effects but documented a perceived positive treatment effect as reported by parents/carers, and the remaining two case reports described improvements.[vii] A randomised placebo-controlled trial was conducted to investigate the efficacy of NMES and TES in 60 children with cerebral palsy.[viii] The electrical stimulation was only tested in legs with two electrodes (one proximal and one distal position). After 16 weeks of treatment, no differences were observed for strength or function. However, statistically significant differences were observed between NMES and TES versus placebo for impact of disability, and the difference continued at the 6 week follow-up between TES versus placebo.

1.1 General Introduction

The Mollii suit is a new technology of electrical stimulation in the form of whole-body garment with multiple electrodes individually programmed to stimulate the selected muscles. Based on preliminary studies, it is suggested that the Mollii suit improves spasticity. Recent studies also proposed that it improves mobility, gait, function and quality of life. However, these studies are based on qualitative and subjective measures.

1.2 Rationale and Justification for the Study

Living with CP is challenging for the child as well as the family charged with their care and support needs. Many families seek effective and sustainable interventions to improve gait of their children with CP. Many families, however, are unable to adhere to frequent intensive centre-based therapy in view of its high cost and time commitment. An intervention that could be used at home, assessed periodically by health care professionals of a tertiary pediatric centre, that has a benefit on gait and motor function in children with CP might be feasible to families in the local Singapore healthcare setting.

1.2.1 Rationale for the Study Purpose

Considering the potential of the Mollii Suit and the need for evidence, we aim to study the effectiveness in improving gait and the feasibility with the use of the Mollii suit in children with cerebral palsy in Singapore.

1.2.2 Rationale for Doses Selected

Preliminary studies have shown that the Mollii suit is effective with one hour every day to every other day use for as 2-8 weeks. After discussion with the industrial partner and with the primary objective of a change in gait in mind, a dosage of 1 hour every day for 4 weeks was decided.

1.2.3 Rationale for Study Population

Studies have shown that the Mollii suit was effective in improving spasticity and reducing pain in adults post stroke and children with cerebral palsy.[ix,x,xi,xii,xiii] As we are studying improvement in gait, ambulant children with cerebral palsy is the target population and they have spasticity as their dominant motor feature.

1.2.4 Rationale for Study Design

This is a single-centre study that compares subjects before and after the intervention. As a wide range of age group is used in the study population, comparison is made in gait in the same individual.

2 HYPOTHESIS AND OBJECTIVES

2.1 Hypothesis

The Mollii suit is effective in improving gait in ambulant children with cerebral palsy

2.2 Primary Objectives

The primary objective is to assess the effectiveness of the Molli suit in improving gait in children with cerebral palsy, GMFCS I-III.

Change in Gait Profile Score will be computed as primary outcome measure. Other measurements obtained in the gait analysis include Gait deviation index, gait speed and cadence etc.

2.3 Secondary Objectives

The secondary objective is to evaluate the acceptability, tolerance and compliance of the Mollii suit in children with cerebral palsy.

2.4 Potential Risks and Benefits:

2.4.1 Potential Risks

Mollii suit may cause discomfort or tingling sensation to some people. Some people may have allergic reaction to the material of the suit. Otherwise, there is minimal risk in wearing the suit if

there are no contraindication.

2.4.2 Potential Benefits

The Mollii suit is potentially an effective adjunct intervention for children with cerebral palsy that can benefit gait and motor function. It can potentially reduce number of visits needed to tertiary hospital as the intervention can be performed at home. It will also reduce reliance on hospital based care and improve convenience for families.

3 STUDY POPULATION

3.1 List The Number and Nature of Subjects to be enrolled

This is a single centre study that will enrol up to 20 children with cerebral palsy.

3.2 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.

3.3 Inclusion Criteria

- Aged 4-18
- GMFCS level I to III
- Spasticity as the dominant motor feature
- Children agree to wear the Mollii suit as per procedures and consent to the study
- Parents/carers agree to assist their child to wear the Mollii suit as per procedures
- Medical practitioner's approval

3.4 Exclusion Criteria

- Individuals with electrical implanted stimulatory device
- Individuals with medical devices that are affected by magnets, such as programmable shunts.
- Individuals with cardiovascular diseases, infectious diseases, malignance (cancer), fever, pregnancy, rashes or skin problems.
- Individuals who have had Botulinum toxin done 6 months prior intervention or soft tissue release surgery done 6 months prior intervention.
- Individuals who have had change in oral medication for spasticity 1 month prior intervention.

3.5 Subject Replacement

Subjects who drop out will not be replaced.

4 STUDY DESIGN

This study will evaluate the effectiveness of improving gait with the use of the Mollii suit in children

with cerebral palsy with instrumented 3-dimensional gait analysis and objective standardised assessment tool at pre-intervention and at 1 month post intervention.

This study will evaluate change in gait and function following a four week intervention period using a protocol of wearing the Mollii suit for one hour every day for four weeks.

This study also evaluates the feasibility of the use of the Mollii suit intervention protocol by conducting qualitative interviews with parents immediately and 1 month after the intervention. Information on compliance, perception of acceptability, benefits or concerns, practicalities, cost and likelihood of using the intervention in the future will be collected.

4.1 Randomisation and Blinding

Randomisation and blinding will not be performed.

4.2 Contraception and Pregnancy Testing

Not applicable.

4.3 Study Visits and Procedures

Table 1: Assessment timeline and persons reporting or conducting the assessments.

	Parent	Child	Assessor	Measure
At Baseline				
Demographics, resource use questionnaire	X	X		Questionnaire
Instrumented 3D Gait analysis		X	X	Gait kinetics and kinematics
EQ-5D	X	X		QoL/ health status
ICF	X		X	Performance/Body structure & function
GMFM		X	X	Performance/ activity (ICF)
FAQ	X	X	X	Performance/Body structure & function
10m walk test		X	X	Performance/ activity (ICF)
GAS	X	X	X	Expectation
Daily during the 4 week intervention				
Study Diary- compliance; activity;	X			
Pain	X	X		
Immediately post intervention				
Instrumented 3D Gait analysis			X	Gait kinetics and kinematics
EQ-5D	X	X		QoL/ health status
ICF	X		X	Performance/Body structure & function
GMFM		X	X	Performance/ activity (ICF)
FAQ	X	X	X	Performance/Body

				structure & function
10m walk test		X	X	Performance/ activity (ICF)
GAS	X	X	X	Expectation
Feasibility/ Acceptability	X			Questionnaire
1 months post intervention				
EQ-5D	X	X		QoL/ health status
ICF	X		X	Performance/Body structure & function
GMFM		X	X	Performance/ activity (ICF)
FAQ	X	X	X	Performance/Body structure & function
10m walk test		X	X	Performance/ activity (ICF)
Feasibility/ Acceptability	X			Questionnaire

4.3.1 Screening Visits and Procedures

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

4.3.2 Study Visits and Procedures

Baseline

Prior to commencement of intervention (within 2 weeks prior to fitting of Mollii suit), the child will undergo:

I. An instrumented 3-dimensional gait analysis

For the 3-dimensional gait analysis, patient is required to walk on a walkway of approximately 8 to10 metres long with 2 force-plates along the walkway. The patient will have skin markers placed on their body, majority on the lower extremities following the Plug-in Model marker placement model by physiotherapist. The patient will be required to walk barefoot with and/or without walking aid repeatedly along the walk-way until 6 to 8 successfully clean strike on the force plate. The VICON infra-red camera system will capture the trial and after which, the data will be analysed by the study team member.

II. **Questionnaire** (Annex I and II)

This consists of 2 sets of self-administer questionnaire for parent and child respectively. The child's questionnaire on demographics, patient's perception on own health, mobility, emotions, activity (EQ-5D, ICF see below) and pain. The parent's questionnaire consist items on demographics, parent's perception on child's health, mobility, emotions, activity and resource use.

III. EuroQoL (EQ-5D)

EQ-5D is a standardised measure of health status in order to provide a simple, generic measure of health for clinical and economic appraisal.[xiv] The EQ-5D-Y is the child-friendly

version. EQ-5D consists of the descriptive system and the EQ visual analogue scale (EQ VAS). The descriptive system comprises 5 dimensions. The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. Parent or caregiver will be answering EQ-5D based on what they think the child feels. Whenever possible, for a child who can communicate and self-report assessment, EQ5D-Y will be used.

IV. ICF-CY

The WHO International Classification of Functioning, Disability and Health, Children & Youth version (ICF-CY) is a measure to grade function of activities of daily living (ADLs).[xv] Few ICF-CY categories have been selected and graded based on the frequency, intrusiveness or severity of the specific impairment. (refer Table below).[xvi]

The ICF-CY categories assessed and grading for each patient before and after intervention

ICF-CY categories	Illustration of grading
D420 Transferring oneself	0 = No impairment/ difficulty 1 = mild impairment/ difficulty (present <25% of time, intensity is tolerable, rare) 2 = moderate impairment/ difficulty (present <50% of time, intensity is interfering in day-to-day life, occasional) 3 = severe impairment/ difficulty (present >50% of time, intensity partially disruptive, often) 4 = complete impairment/ difficulty (present >95% of time, intensity totally disruptive, constant) 8 = not specified (insufficient information) 9 = not applicable
D4153 Maintaining a sitting position	
B1340 Amount of sleep	
B1342 Maintenance of sleep	
B1261 Agreeableness	
B7356 Tone of all muscles of the body	
B7650 Involuntary contractions of muscle	
B2800 Generalised pain	

V. **Gross Motor Function measure (GMFM)** (ANNEX VIII)

The Gross Moor Function Measure (GMFM) is an assessment tool designed and evaluated to measure changes in gross motor function over time or with intervention in children with cerebral palsy[xvii].

VI. **Functional Assessment Questionnaire (FAQ)** (ANNEX VIII)

The Functional Assessment Questionnaire (FAQ) is a 10 point scale (6–10 describe functional walkers with 10 being most able) which was designed specifically to be used as an outcome measure in individuals with physical disability.[xviii]

VII. **10 Metre Walk Test** (ANNEX VIII)

The 10 Metre Walk Test is a performance measure used to assess walking speed in metres per second over a short distance. It can be employed to determine functional mobility and gait.[xix]

VIII. **Goal Attainment Scale (GAS)** (ANNEX VIII)

GAS is an individualised outcome measure involving goal selection and goal scaling that is

standardised in order to calculate the extent to which a patient's goals are met.[xx]

Fitting

Child will be fitted with the Mollii suit and settings will be programmed by the Mollii suit company, Inerventions. The suit will be administered by trained physiotherapists from KKH. Child brings the Mollii suit home.

Intervention

Throughout the intervention period of 4 weeks, child will be wearing the Mollii suit for 60 min/ day every day. Parent will be keeping logs of compliance use, activity and adverse effect daily during this period. Child will be using the log book to document pain during this period. (Annex III)

Post-intervention

Immediately after intervention, child will undergo instrumented 3- dimensional gait analysis and objective assessments. Child and parent complete a questionnaire (Annex IV and VI) on health outcome measures and feasibility/ acceptability outcomes (refer Table 1).

1 months after intervention period, child will undergo objective assessments. Child and parent complete a questionnaire (Annex V and VII) on health outcome measures and feasibility/ acceptability outcomes (refer Table 1).

Table 2: SUMMARY OF STUDY VISITS

VIST 1:	Pre-intervention assessments: - Instrumented 3-dimensional gait study - Questionaires (include EQ-5D, ICF) - GMFM - FAQ - 10m walk test - GAS	Patient will be charged for one PT session per standard care. Gait study is FOC
VISIT 2:	Collection of Mollii suit, settings for Mollii suit Signing of loan agreement	
@HOME 4WEEKS	Patient will wear Molli suit at home daily 1 hour for 4 weeks. Patient/ parent keep log logs of compliance use, pain and adverse effects.	
VISIT 3	Return Mollii Suit Post-intervention assessments: - Instrumented 3-dimensional gait study - Questionaires (include EQ-5D, ICF) - GMFM	Patient will be charged for one PT session per standard care. Gait study is FOC

	- FAQ - 10m walk test - GAS	
VISIT 4 (1 MTH LATER)	1month post-intervention assessments: - Questionaires (include EQ-5D, ICF) - GMFM - FAQ - 10m walk test	Patient will be charged for one PT session per standard care.

4.3.3 Final Study Visit:

As per section 4.3.2

4.3.4 Post Study Follow up and Procedures

Immediately after intervention, child will undergo instrumented 3- dimensional gait analysis and objective assessments, and complete a questionnaire on health outcome measures and feasibility/ acceptability outcomes.

1 months after intervention period, child will undergo objective assessments, and complete a questionnaire on health outcome measures and feasibility/ acceptability outcomes.

4.4 Discontinuation/Withdrawal

4.4.1 Discontinuation Criteria

Study intervention will be discontinued if subject is unable to tolerate the Mollii suit.

4.4.2 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. No gait analysis and other objective assessments will be done.

5 TRIAL MATERIALS

5.1 Trial Product (s)

The Mollii suit
The Molli suit is an innovative approach for non-invasive, electrical stimulation with multiple electrodes incorporated in a whole-body suit.[xxi] It is a transcutaneous electrical stimulation therapy which is at the 'sub-sensory level' and involves e-stim above the threshold for feeling the stimulation but below the threshold to get a muscle contraction.

HSA approval
The Mollii suit is an electrical and neuromuscular stimulator classified as a class IIa medical device. Approval from Health Science Authority Singapore has to be obtained.

Technical Information of the Mollii suit:
- Power supply – 4 AAA batteries
- Voltage – 20V
- Pulse width – 25-175 us
- Frequency - 20Hz
- Pulse appearance - square wave
- Channels – 40
- Electrodes – 58
- Electrode material Silicone rubber
- Fabric material – Nylon 82%, Spandex 18%

5.2 Storage

The Mollii suits will be stored in a locked cupboard in Rehabilitation department.

6 TREATMENT

6.1 Rationale for Selection of Dose of Intervention

Preliminary studies have shown that the Mollii suit is effective with one-hour every day to every other day use for as 2-8 weeks. After discussion with the industrial partner and with the primary objective of change in gait in mind, a dosage of one hour everyday use for 4 weeks was decided.

6.2 Intervention settings

The intervention is the Mollii suit which is fitted and programmed by the Mollii suit distributor, Inerventions, and will be administered by trained physiotherapists from KKH.

6.3 Intervention Administration

Participants will be involved in the Intervention phase of the study for 4 weeks with treatment duration of 60 min/ session every day.

6.4 Specific Restrictions / Requirements

Nil as long as exclusion criteria is not met.

6.5 Blinding

Blinding is not done.

6.6 Concomitant therapy

Subjects can continue regular standard care.

7 SAFETY MEASUREMENTS

7.1 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

7.2 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.

7.3 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.

7.4 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.

7.5 Complaint Handling

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

8 DATA ANALYSIS

8.1 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.

8.2 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.

9 SAMPLE SIZE AND STATISTICAL METHODS

9.1 Determination of Sample Size

Sample size is determined based on a two-sided paired t-test at 80% power and significance level of 0.05 to detect a minimal clinically important difference of 1.6 in Gait Profile Score with a standard deviation of 2.4 between pre- and post-intervention.

9.2 Statistical and Analytical Plans

Descriptive analysis of demographic and outcomes measures will be conducted. Mean, median, standard deviations, and proportions will be calculated to describe the samples.

Sample size is determined based on a two-sided paired t-test at 80% power and significance level of 0.05 to detect a minimal clinically important difference of 1.6 in Gait Profile Score with a standard deviation of 2.4 between pre- and post-intervention.

10 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.

11 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.

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

12.1 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.

12.2 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.

13 PUBLICATIONS

Study findings will be written up in a manuscript and published in a peer-reviewed journal. The publication policy will cover authorship, acknowledgments, and review procedures.

14 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.

15 FUNDING and INSURANCE

FUNDING AND RESOURCES

In cash:

Item	Total
Total cash needed for Gait Analysis x 20 subjects	$62,960

KKH Research Grant will cover SGD $34,988.

Inerventions, Mollii will fund remaining SGD $27,972.

In-kind contributions:

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

Mollii will supply up to 16 Mollii suit/ 10 control units for the participants during the study period.

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