NHS
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TRIAL PROTOCOL:

How does selective motor control and knee extensor strength impact on crouch gait in children with cerebral palsy during an everyday walking circuit?

The RAINCOAT study:

EVERYDAY WALKING IN CROUCH GAIT in children with cerebral Palsy

PROTOCOL VERSION NUMBER: v4

DATE: 19/05/22

NHS
Health Research Authority

This protocol has regard for the HRA guidance and order of content

RESEARCH REFERENCE NUMBERS:

IRAS number: 313063

/ CO-SPONSORS / JOINT-SPONSORS

TRIAL REGISTRY NUMBER AND DATE

OTHER RESEARCH REFERENCE NUMBERS

SPONSOR number

FUNDERS number

SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031), amended regulations (SI 2006/1928) and any subsequent amendments of the clinical trial regulations, GCP guidelines, the Sponsor's (and any other relevant) SOPs, and other regulatory requirements as amended.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies and serious breaches of GCP from the trial as planned in this protocol will be explained.

For and on behalf of the Trial Sponsor:

Signature: ..... Date: ...../...../.....

Name (please print):

Position:

University Sponsor Representative.

Signature: ..... Date: ...../...../.....

Name: (please print): XXX

Position Chief Investigator

KEY STUDY CONTACTS

Chief Investigator	Prof Jon Marsden University of Plymouth PL4 8AA jonathan.marsden@plymouth.ac.uk
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Funder	Torbay medical research Fund admin.torbaymrf1@nhs.net

Contents

LIST OF ABBREVIATIONS

AE	Adverse Events
CDC	Child Development Centre
CI	Chief Investigator
CP	Cerebral Palsy
CRF	Case Report Form
EMG	Electromyography
EWT	Everyday Walking Task
GMFCS	Gross Motor Function Classification System
ICF	Informed Consent Form
MRC	Medical Research Council
NHS	National Health Service
PIS	Participant Information Sheets
PI	Principal Investigator
PROM	Passive Range of Motion
REC	Research Ethics Committee
SAE	Serious Adverse Event
SCALE	Selective Control Assessment of the Lower Extremity
SHP	School of Health Professions
SMC	Selective Motor Control
SMG	Study Management Group
SOP	Standard Operating Procedure

SC	Study Co-ordinator
SSC	Study Steering Committee
TDC	Typically Developing Children

TRIAL SUMMARY

StudyTitle	How does selective motor control and knee extensor strength impact on crouch gait in children with cerebral palsy during an everyday walking circuit?	
Internal ref: **Short Title**	(this will come from university ethics) The **RAINCOAT** study: EVE**R**YDAY W**A**LK**I**NG A**N**D **CRO**UCH G**AIT** in children with cerebral palsy	
Study design	Cross-sectional observational study	
Study participants	Children with Cerebral Palsy and Typically Developing Children aged 6-18years	
Planned Sample size	40	
Study Duration	90 minutes	
Planned Study Period	1st November 2022 to 31st January 2024	
	Objectives	Outcome Measures Completed in one study visit
1.	To explore how variance of knee flexion at initial contact and midstance in children with cerebral Palsy (with and without crouch gait) across 5 Everyday walking trials is best explained by two of the following variables: selective motor control, knee extensor strength, knee flexor strength and knee flexor stiffness	• Selective Motor Control using Selective Control Assessment of the Lower Extremity (SCALE) • Knee extensor strength, Knee flexor strength, and Knee flexor stiffness using dynamometer • Knee Flexion Angle at Initial Contact and Midstance using Promove, inertial sensors
1.	To measure and compare Selective motor control in children with Cerebral Palsy, with and without crouch gait, and in typically developing children.	• Selective Control Assessment of the Lower Extremity (SCALE) • Passive Range of motion of the ankle with goniometer
2.	To measure and compare isometric and isokinetic knee extensor strength in children with	• Maximal Isometric and Isokinetic Knee

	Cerebral Palsy, (with and without crouch gait) and in typically developing children.	Extensor strength using a dynamometer
4.	To measure and assess Isometric knee flexor strength in children with Cerebral Palsy (with and without crouch gait) and in Typically developing children	• Maximal isometric knee flexor strength using a Dynamometer
5.	To measure and assess knee flexors passive stiffness, and stretch mediated stiffness, in children with Cerebral Palsy (with and without crouch gait) and in Typically developing children.	• Passive and stretch mediated stiffness of the knee flexors measured using a Dynamometer • Passive Range of Motion - Popliteal angle with Goniometer.
6	To measure and analyse amplitude and variability of knee flexion during Initial Contact and Midstance in children with Cerebral Palsy, (with and without crouch gait) and Typically Developing Children across five everyday functional walking tasks	• Knee Flexion Angle at Initial Contact and Midstance using Promove, inertial sensors

FUNDING AND SUPPORT IN KIND

FUNDER(S)	FINANCIAL AND NON-FINANCIAL SUPPORT GIVEN
Torbay Medical research Fund admin.torbaymrf1@nhs.net	Financial Support of the study via a clinical doctoral fellowship which includes the cost of the backfill for my clinical hours.
University of Plymouth	Academic Support

ROLE OF TRIAL SPONSOR AND FUNDER

The Sponsor organisation is University of Plymouth. The Sponsor Representative is Sarah Jones. Research Governance Specialist, -University of Plymouth. The sponsor's responsibilities are as defined in the UK policy framework for health and social care research (version 3.3 2017).

Tasks associated with meeting various sponsorship responsibilities have been delegated to the CI or by way of formal agreement.

Torbay Medical Research Fund, funds this study as part of a Clinical Doctoral Fellowship. The role of the funder is to fund the trial. The Sponsor nor funder have no direct role in trial design, data analysis and interpretation, manuscript writing or dissemination of results.

ROLES AND RESPONSIBILITIES

Study Steering Committee and study management group

The Study Steering Committee (SSC) will consist of Harriet Hughes' supervisory team, Prof Jon Marsden, Dr Cherry Kilbride and Rachel Rapson, a patient representative and an independent specialist physiotherapist with research training.

The study management group will consist of Harriet Hughes' supervisory team, Prof Jon Marsden, Dr Cherry Kilbride and Rachel Rapson.

Frequency of Meetings

The SSC will meet on a 3 monthly basis

The study management group will meet on a monthly basis .

Responsibilities

The SSC will meet on a 3 monthly basis (via Microsoft teams or face to face) and provide oversight of the study (adverse events , withdrawals and/or declines, adherence to planned timelines, finances and recruitment rates and dissemination plans).

The study management group will meet on a monthly basis and discuss the everyday running of the study as well as adverse events.

Protocol Contributors

Harriet Hughes is the Study Co-ordinator and Doctoral Research Fellow and has shared responsibility for the implementation of this study in conjunction with the Chief investigator, Prof Jon Marsden. Harriet Hughes (SC) has responsibility for preparing the protocol, writing, and submitting the ethics and HRA applications, preparing periodic reports, recruitment, and clinical oversight of the safety of patients participating in the study, including an ongoing review of the risk and/or benefits. She will also take the lead on data analysis and article publication. She is an experienced Paediatric Physiotherapy Clinician undertaking doctoral-level studies while employed by the NHS and the University of Plymouth.

Jon Marsden is Professor of Rehabilitation University of Plymouth and is the Chief Investigator of this study . He will be first supervisor for the part-time PhD studies of Harriet Hughes the Study Co-ordinator and will provide guidance on the protocol; management of the study, data collection and analysis and write up and dissemination

Dr Cherry Kilbride, Brunel University, London. She will act as a co-investigator to the trial and overall as a second supervisor for the part-time PhD studies of Harriet Hughes. She will also provide

guidance on the protocol; management of the study, data collection and analysis and write up and dissemination.

Rachel Rapson, NIHR Doctoral Fellow and Clinical physiotherapy Manager, Torbay and South Devon NHS Trust. She will act as a co-investigator to the trial and overall, as a third supervisor for the part-time PhD studies of Harriet Hughes. She will also provide guidance on the protocol; management of the study, data collection and analysis and write up and dissemination.

Patient representative will provide advice on the study protocol, patient/public facing documentation, recruitment, timelines, adverse events and finances and dissemination

The independent academic physiotherapist will provide advice on the study protocol, recruitment, and timelines, adverse events and finances and dissemination.

KEY WORDS

Cerebral palsy, crouch gait, selective motor control, knee extensor strength, knee flexor strength, knee flexor spasticity.

1.BACKGROUND

Cerebral Palsy (CP) is a neuromotor disorder that affects the developing fetal or infant brain and has prevalence of between 2 and 3 per 1000 births worldwide (Rosenbaum *et al.*, 2007). Although the injury to the brain is non-progressive the functional impairments associated with CP are progressive in nature, resulting in interrelated neuromuscular impairments such as muscle weakness, spasticity and reduced selective motor control; these significantly impact on a child's walking pattern and community participation (Noorkoiv *et al.*, 2019) .

The functional ambulatory status of children with CP is assessed using the Gross Motor Function Classification System (GMFCS). This is a five-level scale; children with GMFCS level I-II walk independently with some limitations, children with GMFCS level III use a walking aid and children with GMFCS level IV and V are reliant on a wheelchair. This study will focus on ambulant Children with CP, GMFCS level I to III (Kedem & Scher, 2016).

Crouch gait is the most common gait problem, affecting 72-76% of ambulant children with bilateral CP (Wren, Rethlefsen & Kay, 2005). This highly inefficient, tiring gait pattern is characterized by excessive knee flexion during stance phase of gait and if left untreated can lead to chronic knee pain (O'Sullivan et al., 2018). Once 30^{o} knee flexion while walking is reached, the degree of crouch rapidly progresses leading to the child requiring wheelchair use for mobility (Galey et al., 2017). The cause of Crouch gait is unclear and is multifactorial in nature, with potential factors including but not limited to, knee extensors weakness , excessive tibial torsion, knee flexor spasticity and contracture and impaired Selective Motor Control (SMC) (O'Sullivan et al., 2018 , Kedem & Scher, 2016) .

SMC is classified as a negative motor sign and when impaired it is defined as 'the inability to isolate the activation of muscles in a selected pattern in response to demands of a voluntary

posture or movement' (Sanger *et al.*, 2006). A recent cross-sectional study found a significant relationship between SMC, as measured by SCALE (Selective Control Assessment of the Lower Extremity), and knee flexion angle during both initial contact and midstance, in children with bilateral spastic CP (Zhou et al., 2018).This suggests that SMC may affect the ability of children with crouch gait to extend the knee during stance phase of gait, when the ankle is dorsiflexed (Zhou *et al.*, 2018). However, this study failed to include a measure of muscle strength, making it difficult to identify if SMC is affecting the ability of the knee to extend, when the ankle is dorsiflexed, or whether this simply due to the inability of weak knee extensor muscles to activate (Sanger *et al.*, 2006). In reality, due to the mulitifactoral nature of crouch a contribution of different neuromuscular impairments is likely. To examine this further, this observational study will explore how both SMC and knee extensor strength impact upon crouch gait.

To date, research has been unable to decipher whether knee extensor weakness may be a contributory cause or a consequence of crouch gait. Findings from modelling studies indicate both, suggesting lower limb extensor strength is needed to help prevent crouch (Arnold *et al.*, 2005) but also that significant quadriceps strength is needed to sustain an upright posture during crouch (Katherine M. Steele *et al.*, 2012). This is supported by studies utilising electromyography (EMG), which indicate significant quadriceps activity is needed to maintain a crouch position (Hsu et al., 1993). This is fits with the findings from Shin et al.(2016), who found that peak isometric strength of the knee extensors was related to knee flexion at initial contact (r= 0.477, p=0.018) and minimum knee flexion in stance (r=0.527, p=0.012) in ambulant children with flexed knee gait. However, these studies did not assess ability of the quadriceps to generate force throughout range of motion, particularly when the knee is nearing full extension (termed inner range). Weakness in inner range may contribute to the cause of crouch (Steele et al., 2012b).

Interestingly, studies investigating the short-term effect of knee extensor strength training on crouch gait have produced inconsistent results (Steele et al., 2012). Some studies report that strength training leads to improvements in knee extension during gait in some children with CP (Steele et al., 2012a, Damiano et al., 1995., Damiano et al., 2010) and others reporting no change (Fosdahl et al., 2019). These intervention studies may indicate that restoring isolated muscle strength on its own may not be enough to improve crouch gait without also assessing and addressing impairments of spasticity and SMC (Steele et al., 2012b).

To date the impact of quadriceps strength in conjunction with SMC and spasticity on crouch gait has yet to be explored, identifying a need for this observational study. Furthermore, those studies that have examined the impact of quadriceps strength on crouch gait have primarily focused on measures of Isometric strength testing through the use of dynamometry (Steele et al.,2012a, Shin et al., 2016)) neglecting the impact of quadriceps strength throughout knee range of movement and providing minimal insight into muscle strength during gait and dynamic walking activities. In addition, many studies exploring factors affecting crouch gait in children with CP have focused on level walking surfaces,

using 3D gait analysis, which tell us little about a child's everyday walking ability, where children often encounter slopes, steps and kerbs.

To address the short comings of previous research this observational study aims to explore how both SMC and quadriceps strength affect crouch gait during an everyday walking circuit. Together this research design will improve our understanding of the relationship between impairments of SMC and quadriceps weakness on crouch gait, as well as limitations on activity and participation in children with CP, enabling the development of new targeted intervention approaches for the community setting.

Using a cross-sectional design, children with CP and crouch gait and matched health controls will be invited to participate in this observational study. Quadriceps strength and hamstring spasticity will be assessed in a laboratory setting using Biodex isokinetic muscle testing machine and SMC will be assessed using SCALE in both children with CP and TDC. Both groups will also be asked to complete an everyday walking circuit in the laboratory, which includes a 10-metre level walkway, a set of 3 steps and walking up and down a slope with a gradient of 1:12, during which, kinematic measures of knee flexion angle during stance phase of gait will be captured using the wearable inertial sensors.

2.RATIONALE

The focus of the proposed study is Children with GMFCS I-III, who comprise of around 67% of the population (about 23,400) of children with CP in the UK. Crouch gait is one of the most common gait deviations found in this population, affecting 72-76% of ambulant children with bilateral CP with the risk of it occurring increasing with age (Rethlefsen *et al.*, 2017). Over time crouch gait leads to higher rates of joint pain, degenerative arthritis and if not adequately treated there is progressive gait deterioration, loss of functional mobility and increasing reliance on a wheelchair for mobility. Although crouch gait may affect relatively small numbers of children, it's impact is felt across a child's lifespan and places a heavy burden on a child's quality of life . Furthermore, the management of crouch gait spans from childhood to old age, requiring multidisciplinary intervention from physiotherapists, orthotist and Orthopaedic surgeons, at a significant cost to the NHS.

At present, the treatment of crouch gait is dominated by surgical interventions with hamstring lengthening being the most frequently used approach (Kedem & Scher, 2016). This is usually performed in the later stages of childhood to prolong independent ambulation and when conservative treatment options are exhausted. Interestingly, despite its wide use clinically, modelling studies suggest that short hamstrings may not be the primary cause of crouch gait and there is evidence to suggest that hamstring lengthening may further weaken weak muscles, increase anterior pelvic tilt and contribute towards back pain (Kedem & Scher, 2016). Furthermore, rates of hamstring lengthening revision are high, due to its limited effectiveness and a return of the crouch gait pattern (Kedem & Scher,

2016a). This places a heavy financial burden on the NHS and is costly to both children and parents alike, who experience disruptions to their home and school life.

Conservative approaches to the management of crouch gait include botulinum toxin injections to the hamstrings, the prescription of orthosis and/or strength training of the lower limb extensor muscles (Galey *et al.*, 2017). Evidence suggests that their effectiveness is usually short term, with inconsistent and/or variable outcomes on crouch (Galey et al., 2017). The limited availability of successful conservative interventions for children with crouch gait means that surgery is almost inevitable, particularly if these children are to remain ambulatory into adolescence and even then, the rate of ambulatory decline in adults with CP is prolific (Galey *et al.*, 2017).

The lack of successful intervention and high rates of ambulatory decline, highlight the need for further research into the multifactorial nature of crouch gait. So far interventions to improve crouch gait have focused on reducing spasticity, lengthening tight muscles and strengthening weakened muscles and very limited attention has been paid to the role of SMC. Research into interventions to improve crouch, as well as modelling studies to examine the mechanism behind crouch, have focused on how these factors impact upon gait kinematics and kinetics using 3D gait analysis. This negates what is most important to children and their families, which is looking at how these multiple factors effect crouch in everyday walking activities, such as slopes and stairs and its impacts on children's community participation.

Therefore, using a cross-sectional study design we aim to examine how SMC and quadriceps strength and hamstring stiffness and spasticity impact on crouch gait in children with CP during an everyday walking circuit compared to a control group of typically developing children.

3.OBJECTIVES

Determine how variance of knee flexion at initial contact and midstance in children with cerebral Palsy (with and without crouch gait) across 6 Everyday walking trials is best explained by the following factors affecting crouch gait:

- selective motor control
- knee extensor strength
- knee flexor strength
- knee flexor stiffness

4. STUDY DESIGN

This is a cross-sectional study design investigating factors affecting crouch gait in children with CP, both with and without crouch gait and comparing them to TD children. The research question can be framed as follows:

Population: Ambulatory Children with cerebral Palsy 6-18 years old

Comparison - TDC aged 6-18 years

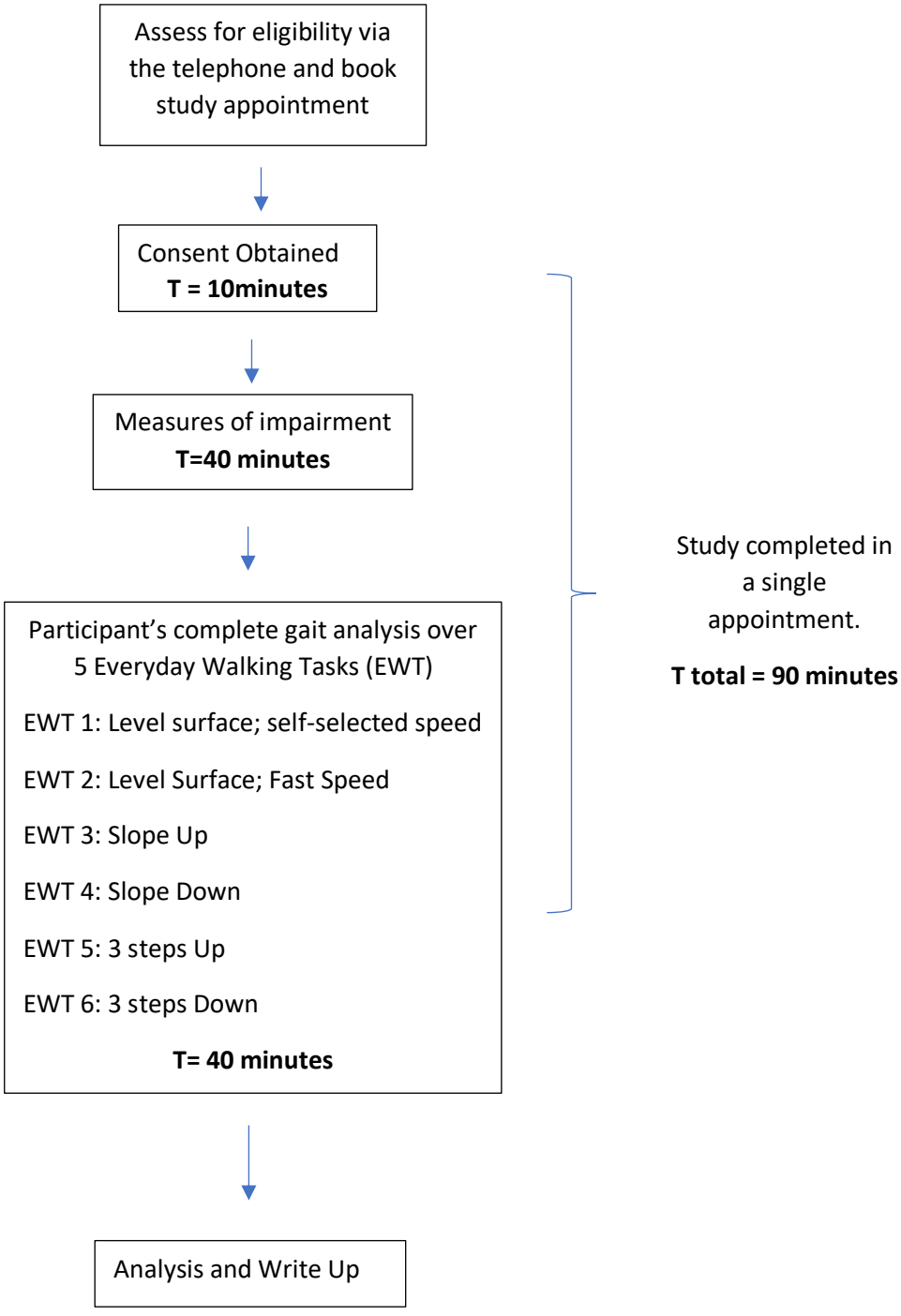
Time: One time study measurement

Predictors: The following potential predictors of crouch gait in everyday walking tasks will be investigated

- Selective motor control, as measured by SCALE
- Isokinetic and Isometrics Knee extensor strength as measured by Dynamometry
- Isometric knee flexor strength as measured by Dynamometry
- knee flexors passive stiffness and stretch mediated stiffness as measured by Dynamometer

Outcome: Crouch Gait as measured by excessive knee flexion (≥ 15˚) at initial contact and midstance whilst walking over a level surface at a self-selected and a fast walking speed, up and down a slope of 7,˚ and up and down 3 steps.

Figure 1. Study flow diagram



5. STUDY SETTING

- This study will take place at the University of Plymouth, Human Movement and Function Lab, based in the School of Allied Health Professions.
- All study measures will be taken and recorded by a member of the research team during a single appointment at the gait laboratory.
- The study will recruit children with CP from Child Development Centres (CDCs) and community settings. These include Torbay and South Devon NHS Trust, Plymouth Hospitals NHS Trust, Royal Cornwall Hospitals NHS Trust.
- Community paediatric physiotherapists and Occupational Therapists will recruit children from their caseloads and Orthopaedic consultants will recruit from their clinic lists
- Typically Developing Children will be recruited through the University of Plymouth and word of mouth.

6. PARTICIPANTS ELIGIBILITY CRITERIA

Inclusion Criteria

1. Diagnosis of spastic CP (GMFCS level I-III), affecting one or more muscle groups in both lower limbs, and aged 6-18years
2. The ability to follow simple instructions
3. The ability to be able to travel to the study site at the University of Plymouth (travel expenses will be provided up to a limit of £30).

   For Typically Developing Children inclusion criteria is that they are aged 6-18 years

Exclusion Criteria

1. Dystonic or Athetoid CP as the sole presentation (children with dystonia / athetosis co-occurring with a spastic presentation can be included)
2. Selective dorsal rhizotomy or Multi level orthopaedic surgery within the last 6 months
3. Soft tissue surgery in lower limbs in the last 6 months.
4. Anti-spasticity botulinum toxin injections within 3 months
5. Moderate to Severe Cognitive Impairment and/or Learning difficulties

   Typically developing children would be excluded if they have a history of cardiovascular, neurological or musculoskeletal disorders

7.STUDY PROCEDURE:

Once children have been recruited to the study they will be invited to their one-off study appointment at the University Of Plymouths; Human Movement and Function Lab (See fig 1: study flow chart). Here consent to participate will be obtained face to face. The SC and research assistant will then take measures of the participants impairments and complete gait analysis over 6 Everyday Walking Tasks (EWT) using the PROMOVE inertial wearable sensors. This will be carried out in a standardised, sequential order, during the same one-off study appointment, within the gait laboratory (See Appendix 2: study protocol flow chart).

7.1 Methods/ Data collection

Participant characteristics

The participants GMFCS level and CP classification and distribution will be established over the initial phone assessment, using the screening tool, this will also identify the participants age and gender and will ensure they meet the study eligibility criteria.

7.3 Measures of impairment

Overview of procedures:

The participant will arrive at the University Of Plymouth; Human Movement and Function Lab. The study will be outlined using the previously supplied information sheets and videos as a guide. Consent will be obtained to participate in the study from parents/guardians. Time will be given for the participants and/or parent/legal guardian to ask questions. Prior to initiating any measures, we will obtain assent from children under the age of 16 years old. Throughout the measures of impairment, the child or young person will be given the opportunity to take comfort breaks. We will also 'check in' with the child during each measure, to ensure they are comfortable, to ask whether they may need a drink or a snack or the opportunity to go to the toilet as well as to check that they are happy to continue with the study. We will inform the child and young person that they can withdraw their participation at any point during the study.

Initially we will measure the participants' height and weight. If the child and young person is happy to do so, we will then ask them to change into shorts. They will then sit on the edge of a plinth, whilst sitting we will then ask them to kick a ball with their preferred leg. This is to establish leg dominance in both the typically developing and CP participants.

The children and young people with CP will then be asked to lie down on a plinth. The study coordinator (SC Hughes) will then carry out manual muscle testing of knee extensor strength using the Medical Research Council Manual Muscle Testing scale (MRC Muscle Scale) and the Ashworth Scale of the knee flexors bilaterally to establish their most affected leg.

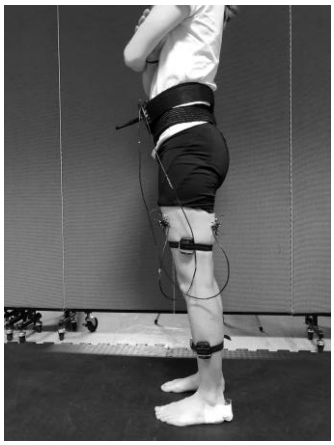
Following this, the participant will be positioned comfortably on the Dynamometer (Biodex system 2, UK) chair with the support of the SC. The SC will then explain how the Biodex Dynanometer works and will also show them the Electromyography (EMG) device. The participant will then be given the opportunity to ask questions about the equipment and given reassurance before any measures are taken. EMG stick on surface electrodes will then be applied to the most affected limb (Quadriceps, hamstrings and gastrocnemius) and attached via leads to a transmitter attached around the waist. Prior to starting the study participants will be asked of any known allergies, this will be captured by the additional information sheet and consent form. In the presence of allergies, Hypoallergenic materials will be used to mitigate any potential skin reaction to the EMG surface electrodes - for further information on mitigating potential skin reactions form the EMG electrodes, please refer to the study Risk Assessment document.

Measures of knee, extensor and flexor strength and stiffness will be taken, using the dynamometer (Biodex system 2, UK). Torque, position, velocity and EMG signals will be Analog-to-digital converted at 2 KHz (power 1401, Cambridge electronic design (CED) UK) and recorded using spike 2 software (CED, UK). The participant will then be repositioned in supine on a plinth. The SC will then explain the clinical measures before measures of SMC and passive range of motion at the ankle and knee are carried out. The SMC will be measured alongside EMG recordings and the assessment videoed to allow offline assessment of muscle activation and SCALE rating.

Once completed, a Promove device (inertia technologies, Netherlands) will be placed around the ankle, knee and hip of the participants most affected leg. EMG recordings using spike 2 software (CED, UK) will be synchronised to the Promove recordings. With bare feet the participant will then complete six everyday walking tasks (6 EWTs). The study is then complete, and the participant will be given the opportunity for debrief. (See Appendix 2– Protocol Flow Diagram)

7.3.1 Strength (A)

Knee extensor and Flexor strength will be measured by a dynamometer (Biodex system 2, Uk). Participants will be sat on an adjustable chair with hips at 85 degrees and the axis of the knee aligned to the axis of the motor (see figure A). The lower leg will be supported by the dynanometer with the foot fixed in an ankle foot orthosis, set at 45 degrees plantarflexion and fastened with a figure of 8 strap. Trunk and Thigh straps will be used to stabilise proximal joints and safety features will include software and hardware stops to prevent excessive joint movement and participants are provided with an emergency cut off switch, to stop the trial at any time.
The following strength test will be undertaken:



A B

Figure 2 A position for testing strength of the knee extensors and hamstring stiffness. Figure B walking assessment using promove sensors (attached to the thigh and shank and heel)

A1. Maximal Isometric strength.

For the Knee extensor this will be assessed with the knee at 90 degrees (Outer range) and 30 degrees knee flexion (inner range). For the knee flexors this will be assessed with the knee at 30 degrees flexion only (outer range).

A2. Maximal Isokinetic strength

Isokinetic Knee extensors strength will be measured through available range, starting at 90 degrees extension and moving at a peak speed of 40 degrees per second. This is based on the average knee velocity during loading and midstance as measured in our previous work with children with CP (Compton MPhil University of Plymouth Unpublished observations).

Both maximum isometric and isokinetic strength will be measured offline using Spike 2 software (Cambridge Electronic Design, UK). The ratio of the knee extensor strength in inner and outer range will also be determined and the degree of EMG co-contraction assessed (percentage activation of quadriceps and hamstrings relative to baseline, resting EMG levels).

7.3.2 Stiffness (B)

B1. Passive Stiffness

Knee flexor passive stiffness will be assessed with the Biodex system, using six, 15-degree amplitude stretches, from a starting position of 90 degrees knee flexion and at a speed of 5 degrees per seconds. Stretches will be separated by between 2-5 seconds, to allow the muscle to relax between each stretch. EMG monitoring will ensure that the muscle is relaxed before a stretch is applied.

B.2 Stretch Mediated Stiffness

Knee Flexor stretch mediated stiffness will also be assessed with the Biodex system using six, 15-degree amplitude stretches, from a starting position of 90 degrees knee flexion. In order to bring about a stretch reflex mediated muscle response this stretch will be carried out at a speed of 75 degrees per second. Again, stretches will be separated by between 2-5 seconds, to allow the muscle to relax between each stretch and EMG monitoring applied to ensure the muscle is relaxed before a stretch is applied.

Total Stiffness

Total Stiffness will be determined from the fast stretch, following removal of torque due to the weight of the leg (estimated via anthropometric data). Offline analysis in Matlab™ will determine the average torque and position in the 300 ms prior to the stretch onset and 300 ms period immediately after stretch offset and manipulandum as:

$$\text{Stiffness} = \frac{Change\ in\ torque}{Change\ in\ position}$$

Passive stiffness (assessed following the 5 deg/s stretch) and total stiffness following the fast stretch will be determined. Stretch Mediated stiffness wil be determined as:

Stretch Mediated stiffness = Total stiffness (fast stretch)- passive stiffness.

Mean EMG amplitude in the hamstrings following the mediated stretch stiffness will be determined. Here the EMG signal will be rectified and the onset and offset of EMG activation determined as the point the signal goes above and below a level (mean baseline period + 4 standard deviations). In total four variables will be assessed (Passive Stiffness, total stiffness, stretch mediated stiffness and EMG amplitude).

An exploratory assessment of activation of the gastrocnemius during muscle stretch tests and stretches will be undertaken. Here the amplitude of the EMG activation during each test relative to resting levels will be measured.

7.3.5 Gait Kinematics during 6 Everyday Walking Tasks (*EWT*)

Gait Kinematics will be recorded with children in bare feet using Promove inertial sensors (Promove Inertia Studios Netherlands ltd). These will be placed on the heel and lateral aspects of the, shank, thigh and posterior aspect of the pelvis (see figure B). EMG recordings using spike 2 software (CED, UK) will be synchronised to the promove recordings(inertia studio software, Netherlands) using trigger pulses generated via the promove inertia gateway.

Promove data will be recorded at 200Hz and exported for offline analysis in matlab. Sagittal plane Euler angles will be determined for the ankle, knee and hip joints and the movement of the pelvis in space will be determined to give an estimate of centre of mass motion.

Participants will the perform the following 6 *EWT*:

EWT 1 - 5metre level walk: Self-selected speed

EWT 2 - 5metre level walk: Fast speed

EWT 3 – 3.6 metre walk slope up (Complies fully with Building Regulations Document M for dwellings)
EWT 4 – 3.6 metre walk slope down

EWT 5 - 3 steps up

EWT 6 - 3 steps down

For safety handrails will be provided for the slope and steps assessment (https://www.disabledaccessramps.net)

Children requiring the use of a walker will use the rails on the steps and slope test and can use their walker on the level surface. A spotter will also provide supervision throughout the EWT. Up to 3 trials will be performed per EWT, to gather a minimum of five steps per task.

The mean amplitude and variability (determined respectively from the mean and standard deviation of 5 steps) of knee flexion in midstance (50% stance phase) and at initial contact will be determined in each condition. Exploratory analysis will assess joint inter-coordination using angle-angle plots. Mean rectified EMG amplitude over a 200 ms window centred on each time point (initial contact and midstance) will be assessed

7.4 Clinical Measures of Impairment

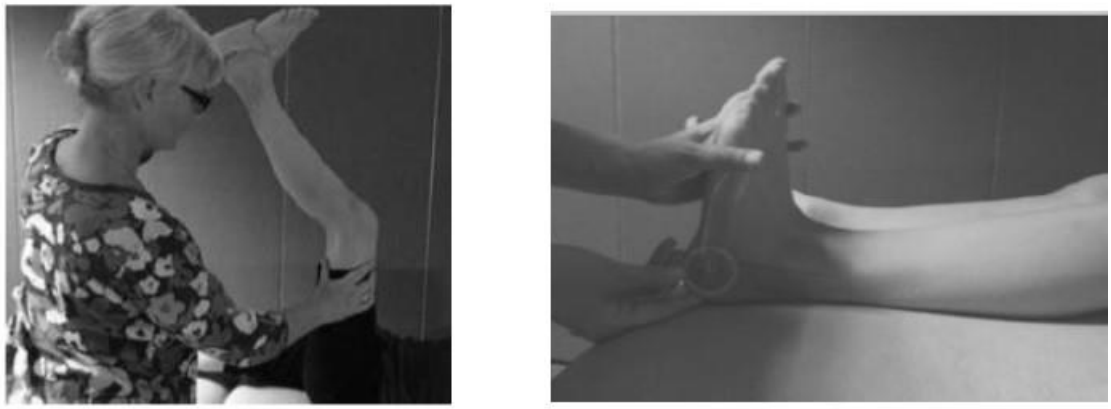
7.4.1 Selective Motor Control (SMC)

SMC will be assessed using the validated, Selective Control Assessment of the Lower Extremity (SCALE) tool. This tool was developed by Fowler *et al.* (2009) for health professionals to clinically assess SMC in the entire lower limb in patients with spastic CP. The SCALE assessment will be completed by the SC with participants positioned on a plinth in sitting, except for the assessment of the hip, which will be performed in side-lying. The assessment will be filmed using 3 static cameras set up to give a 3D view and the video footage will be used by the SC and a blinded assessor to calculate the SCALE score for each participant's lower limb. EMG recordings will be simultaneously assessed to provide an exploratory analysis of muscle activation during this test.

7.4.2 Passive Range of Motion (PROM)

7.4.2 (I) Popliteal Angle

The popliteal angle (assessment of hamstring length) will be obtained from both lower limbs with the participant positioned in supine lying on the plinth. The SC will flex the participants hip to 90 degrees and extend the knee, the research assistant will then record the popliteal angle using a goniometer, in accordance to CPIP measurement guidelines ((APCP, 2017) . This will then be repeated 3 times on each leg, so that an average popliteal angle is obtained for the right and left limb (see figure 3 A).



A B

Figure 3 A Measurement of popliteal angle 3B Measurement of ankle angle

7.4.2 (II) Passive Ankle Range of Motion

The participant will be positioned in supine on a plinth. The SC will extend the knee and dorsiflex the ankle (assessment of Gastrocnemius length), whilst the research assistant measures the degree of ankle dorsiflexion. This will then be repeated with the knee flexed (assessment of soleus length). Both goniometer measurements will be repeated 3 times, so that an average measure of gastrocnemius and soleus length is obtained for each lower limb (see figure 3B).

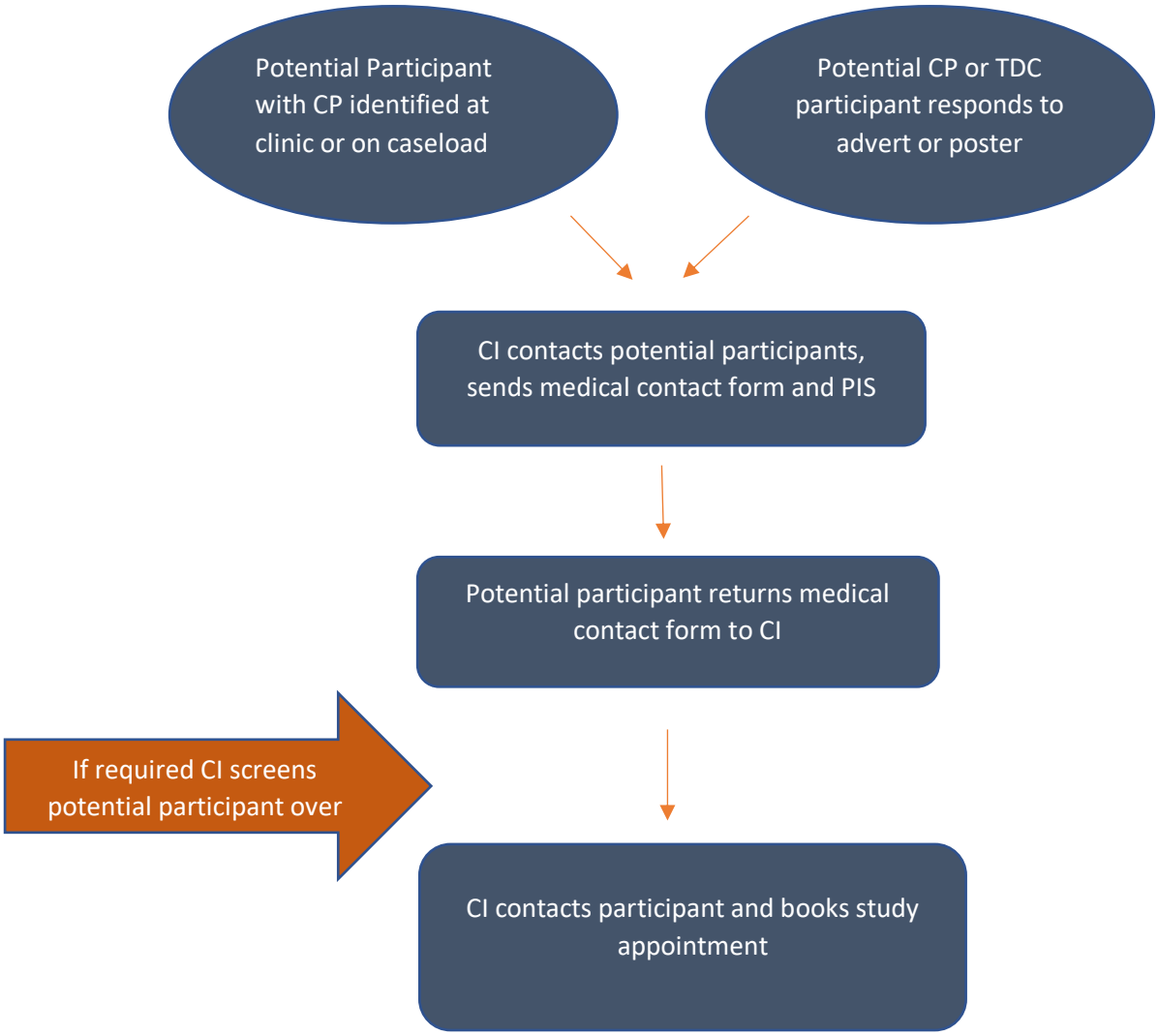
8.RECRUITMENT

Recruitment will take place simultaneously across each Child Development Centres (CDCs) and Community Paediatric Outpatient physiotherapy services. These include Plymouth Hospitals NHS Trust, Torbay and South Devon NHS Trust, Royal Cornwall Hospitals NHS Trust. We will also advertise the study via interest groups, University of Plymouth website

and charity / support group websites (e.g Cerebra). In preparation for recruitment, the CI will visit each site to familiarise physiotherapists with the eligibility criteria and study procedures

Potential study participants will be identified, screened and recruited as shown in Figure 4.

Figure 4. Diagram of recruitment



- Recruitment will take place simultaneously in each NHS trust, the university of Plymouth and via social media
- In preparation for recruitment the SC will visit each recruiting sites to familiarise recruiting clinicians with eligibility and study procedure.

- Once a child has been recruited and identified as a suitable candidate to participate in the study the SC will contact their parents to arrange an appointment for them attend the study assessment at the University of Plymouth

8.1 Estimation of recruitment rate

There are an estimated 1460 children with CP within the targeted age range and severity distribution in the South West of England, based on published prevalence data and population estimates from the Office for National Statistics (2015). Of these 71% of children are predicted to be ambulant, i.e. GMFCS levels I-III. We anticipate that within each NHS trust locality there will be approximately 150 children with a diagnosis of CP (Cerebral Palsy Integrated Pathway South West, 2017 unpublished data). Therefore, we predict that approximately 60-80 ambulant children with CP may be eligible in each NHS trust locality.

We aim to recruit 20 participants with CP across the three sites in Devon and Cornwall over a 6-month period and 20 TDC from the University of Plymouth. An estimated recruitment rate of two to four children per month over a 10-month period has been calculated based on the population and previous experience.

8.2 Participant identification

Recruitment will primarily occur through clinical teams at 3 NHS Trusts: These include Plymouth Hospitals NHS Trust, Torbay and South Devon NHS Trust, Royal Cornwall Hospitals NHS Trust.

Participants will also be recruited via posters and adverts. These will be distributed in local newsletters of groups such as APCP (Association of Paediatric Chartered Physiotherapists) and PenCru (Peninsula Childhood Disability Research Unit). As well as online via social media sites such as facebook, Instagram and twitter on pages that are relevant to our study population, such as Cerebral Palsy UK, Cerebra, CP sport and SCOPE .

- Physiotherapists, occupational therapists, paediatricians and orthopaedic surgeons will identify potential participants during clinics and via their caseload lists. Clinicians may approach children on their caseloads by telephone before sending out an information pack to those who are interested in taking part. The information pack contains a contact reply slip, prepaid envelope and information sheet.
- Posters and leaflets will be produced for clinicians to distribute to potential participants. They will also be issued for clinicians to put up in departments and waiting rooms where children with CP may have appointments.
- Potential participants can contact the research team via contact details on posters / adverts or via a contact reply slip and prepaid envelope which is part of the information pack
- When potential participants contact the research team they will be contacted via their preferred route (eg telephone / e mail) and the participant information sheet

(PIS) will be sent out and later discussed to ensure that the parents / guardian and children understand the study prior to volunteering. The PIS will be available for parents and young adults (16-18 years) and an easy read version will be available for children.

- Consent forms will be provided to parents and, young adults, and assent forms provided to children when attending the appointment.
- Participants / guardians and or parents will be issued with PIS at least 24 hours prior to their study appointment so that they have time to discuss the trial with the research team before participating.

8.3 Screening

The local PI will use a study-specific screening log to record numbers of children eligible, ineligible, the numbers of children approached, and numbers of study information packs given out at each site. Potential participants who respond to the invitation and will be screened for suitability using a telephone questionnaire to check diagnosis, age, GMFCS level, neuromusculoskeletal involvement and distribution and the child's ability to follow simple instructions.

8.4 Payment

Travel expenses (up to £30/visit) will be reimbursed for all assessment sessions. Travel expenses above this amount will be discussed on a case by case basis.

8.5 Consent

- Potential participants/parents and/or guardians will be issued with a PIS
- Discussions will take place between the potential participant, their parent and/or legal guardian and a member of the research team. This will cover the nature of the study, the study procedure, the possible risks associated with participation, as well as their right to withdraw from the study at any time. Potential participants/parents and/or guardians will also be given the opportunity to ask questions.
- According to the Medicines For Human Use (Clinical trials) regulations, children under the age of 16 are prohibited from taking part in a clinical trial without the consent of a parent or legal guardian or representative. Therefore, in children under the age of 16 years old, the child's parents or their legal guardian will be responsible for signing and completing the written consent form. Assent from the child will be obtained through discussion with their parent or legal guardian and the CI.
- Young person's participating between 16 and 18 years of age who are considered capable of giving consent according to the Health Research Authority will have the opportunity to complete their own written consent form.
- Written informed consent and assent will be recorded at the start of the child's study appointment by the CI, before any study investigations can begin.

9. DATA COLLECTION

9.1 Baseline data

- GMFCS level
- Distribution of lower limb weakness
- Date of Birth
- Medical and surgical history
- Height, Weight, pelvic depth

9.2 Outcomes

The trial objectives will be measured using the Outcome measures listed in the table below

Objectives	Outcome Measures Completed in one study visit
Primary Objective	
1. To explore how variance of knee flexion at initial contact and midstance in children with cerebral Palsy (with and without crouch gait) across 5 Everyday walking trials is best explained by two of the following variables: selective motor control, knee extensor strength, knee flexor strength and knee flexor stiffness	• Selective Motor Control using Selective Control Assessment of the Lower Extremity (SCALE) • Knee extensor strength, Knee flexor strength, and Knee flexor stiffness using dynamometer • Knee Flexion Angle at Initial Contact and Midstance using Promove, inertial sensors
Secondary Objectives	
2. To measure and compare Selective motor control in children with Cerebral Palsy, with and without crouch gait, and in typically developing children.	• Selective Control Assessment of the Lower Extremity (SCALE) Passive Range of motion of the ankle with goniometer
3. To measure and compare isometric and isokinetic knee extensor strength in children with Cerebral Palsy, (with and without crouch gait) and in typically developing children.	• Maximal Isometric and Isokinetic Knee Extensor strength using a dynamometer
4. To measure and assess Isometric knee flexor strength in children with Cerebral Palsy (with and without crouch gait) and in Typically developing children	• Maximal isometric knee flexor strength using a Dynamometer
5. To measure and assess knee flexors passive stiffness, and stretch mediated stiffness, in children with Cerebral Palsy (with and without crouch gait) and in Typically developing children.	• Passive and stretch mediated stiffness of the knee flexors measured using a Dynamometer • Passive Range of Motion - Popliteal angle with Goniometer.
6. To measure and analyse amplitude and variability of knee flexion during Initial Contact and Midstance in children with Cerebral Palsy, (with and without crouch gait) and Typically Developing Children	• Knee Flexion Angle at Initial Contact and Midstance using Promove, inertial sensors

across five everyday functional walking tasks	
Exploratory assessment	
Overflow muscle activation during strength tests and stretches	Mean amplitude EMG activation in the gastrocnemius during knee extensor strength tests and hamstring stretches.
Muscle activation during SCALE	EMG amplitude and coactivation in the hamstrings, quadriceps and gastrocnemius during SCALE tasks
Muscle activation during EWT	EMG amplitude and coactivation in the hamstrings, quadriceps and gastrocnemius during EWT

9.3 Outcome Measures

The following assessments will be carried out at the study appointment. This will take approximately 90 minutes to complete (please see flow diagram- Appendix 2)

9.3.1 Primary Outcome

- Walking Kinematic amplitude measured using PROMOVE inertial sensors over 6 Everyday Walking Tasks.

9.3.2 Secondary Outcome Measures

- Walking Kinematic variability measured using PROMOVE inertial sensors over 6 Everyday Walking Tasks.
- SCALE - Selective Control Assessment of the Lower Extremity
- Maximal Isometric and Isokinetic knee extensor strength using Dynamometer (Biodex system 2, Uk) of the most affected limb. Inner and outer range and maximal isokinetic strength.
- Maximal Isometric Knee Flexor Strength using dynamometer (Biodex system 2, Uk) of the most affected limb
- Knee flexor stiffness using dynamometer (Biodex system 2, Uk) of the most affected limb- passive and stretch reflex mediated stiffness and EMG amplitude post-fast stretch
- PROM of the ankle, in a flexed and extended knee position bilaterally using a goniometer
- Popliteal angle of the knee bilaterally using a goniometer

9.3.3 Exploratory Outcome Measures

- Gastrocnemius EMG amplitude will be used to measure over flow activity during strength tests (isokinetic and isometric knee extensor, isometric knee flexor) and fast hamstring stretches.

- Muscle activation during SCALE- EMG amplitude and coactivation in the hamstrings, quadriceps and gastrocnemius will be assessed during SCALE tasks
- Muscle activation during EWT-EMG amplitude and coactivation in the hamstrings, quadriceps and gastrocnemius during EWT tasks

9.4 Withdrawal

Participants can withdraw at any point in the study without giving a reason. It will be emphasised that this would not affect their healthcare or potential involvement in other research. Children's data up to that point will be used for data analysis unless participants express that they would like this data to be destroyed.

10. DATA MANAGEMENT

10.1 Data Collection Tools and source document identification

Study data will be recorded on the trial specific case report forms. The Case report Form (CRF) will be a printed paper document. Data captured on the CRF will be considered source data. The baseline date and outcome measures that will be recorded are outlined in the data management plan.

The study co-ordinator will complete all CRF form for all participants. Completeness of data will be maximised by:

- Checking all forms at the end of the study to ensure no missing items
- Where possible, arranging another assessment session should the participant not attend the scheduled study appointment.

Once study appointment is completed the CRF forms will be signed and dated by the study co-ordinator.

10.2 Participant Numbering

Each participant will be issued a unique participant number when they are registered onto the study.

10.3 Archiving

Paper and electronic formats and essential study documentation (i.e content of Study Master file) will be store in a secure location for a minimum of 10 years after the end of the study. Archiving will be authorised by the Sponsor following submission of the end of study report. No essential documents should be destroyed unless or until the Sponsor gives authorisation to do so

10.4 Access to Data

Data will be collected and stored in accordance with the Data Protection Act 1998/General Data Protection Regulation 2018. Data generated from this study will be available for inspection on request by the participating research team, Plymouth University representatives, the REC, local R&D Departments and the regulatory authorities.

11. Statistics and Data Analysis

11.1. Analysis of Impairment:

Data will be assessed for normality using a Shapiro-Wilks test. People with CP with and without crouch gait will be compared to TDC using an Analysis of Variance. Significant data will be explored further with post-hoc testing. The following variables will be assessed:

11.1.1 Strength

Isometric knee extensor strength (90 & 30 degrees); Inner and outer range ratio; maximal isokinetic knee extensor strength; maximal knee flexor strength. As strength measures will be related Bonferroni correction will be provided (n=5 variables p=0.05/5=0.001).

11.1.2 Stiffness

Passive stiffness total, stretch reflex mediated stiffness and EMG amplitude in the hamstrings will be analysed with a Bonferroni correction (n=3 variables p=0.05/3=0.0015).

11.1.3 PROM

Ankle range and popliteal angle.

11.1.4 SMC

SCALE is a summated ordinal measure. Therefore groups will be compared using a non-parametric Friedman's test.

11.1.5 Exploratory analysis of muscle activation

Descriptive statistics will be used to describe the mean amplitude of EMG gastrocnemius activation during the knee stretch and strength tests. Mean EMG amplitude during the SCALE test and EWT in the quadriceps and hamstrings will be described.

Participants with CP will be divided into 2 groups those with and without crouch gait as determined by ≥21 degrees of midstance knee flexion during level walking. This cut off is based on the mean + 2 standard deviations of previous data of healthy participants walking (E Compton MPhil University of Plymouth Unpublished observations). Differences between children with / without crouch gait will be summarised using descriptive statistics.

11.2 Analysis of kinematics during Everyday walking tasks:

The amplitude and variability of knee flexion will be compared across groups using a between groups repeated measures ANCOVA with groups being; children with CP crouch gait (Crouch +), Children with CP but not Crouch gait (Crouch -), TDC and factors of the five Everyday walking tasks (EWT 1- level walk: Self-selected speed, EWT2 level walk: fast speed, EWT 3 slope: Up, EWT 4 slope: down, EWT 5 steps: up, EWT 6 steps: down). Mean walking speed will be added as a covariate. Significant data will be explored further with post-hoc testing.

11.2.1 Relationship between impairment and Everyday walking tasks:

The relationship between the mean degree of knee flexion during the everyday tasks and the impairment measures will be assessed. With 20 participants with CP, up to 2 predictors will be entered into a multiple regression. The variables chosen will be determined from those showing the largest difference between the Crouch+ and Crouch – groups in each of the main impairment categories (strength, stiffness and selective motor control).

11.3 Sample size calculation

Previous work has explored factors affecting stiffness gait in children with CP. Twenty Seven pwCP (age 13.6±8.3 years; gender 15 males, 12 females; height 1.4 ±0.2 metres [m]; weight 39.2± 19.4 kilograms [kg]) were compared to 20 controls. Marked differences in knee strength and stiffness (rectus femoris) were seen between TDC and children with CP with minimal effect sizes of 0.68 (range 0.68-2.2). With 18 people in each group it would be possible to detect a minimum effect size of 0.68. To account for 10% data loss in some measures (e.g. due to participants not completing some tests) we will recruit 20 people with CP and 20 people TDC. With 20 people with CP it will be possible to undertake a multiple regression to investigate factors associated with mean knee flexion amplitude during the EWT and up to two predictors (measures of impairment).

12.SAFETY AND MANAGEMENT OF RISK

12.1. Dynamometer (Biodex, Suffolk UK)

The Study Co-ordinator will ensure that the Biodex (Suffolk,UK) is used and set up in accordance to the Standard Operating Procedure. This will ensure that it is set up correctly and will also include a manual handling assessment to help the participant safely transfer into the Biodex chair. Prior to Dynamometer set up a verbal explanation of how the Biodex works will be given to the participant and the parent and/or legal guardian. If the participant remains anxious or concerned, then the research assistant will demonstrate how it is used. The participant will also be made aware of the emergency stop button, so they can stop the Biodex dynamometer at any point. Prior to starting the Dynamometer measurements, the participant will be given the opportunity to ask questions. The Biodex has software and hardware safety features to prevent over stretching muscles and the dynamometer motor exerting too much torque.

12.2. Clinical and walking Measures

Both the CI and Study Co-ordinator will have sufficient training in carrying out the SCALE and PROM measures using a goniometer. The participant will also be given a verbal explanation of what will happen during the clinical measures and they will have the opportunity to stop the assessment at any time. For the clinical measures the participant will position themselves in sitting or lying on a plinth in accordance to what is required for the

assessment. This will be on a height adjustable plinth, allowing for safe transfer on and off the plinth by the participant and enabling the CI and SC to raise the plinth to a suitable height during the assessment, thus reducing manual handling risks. If a participant has difficult moving themselves from lying to sitting they will be assisted by the CI and SC using appropriate risk assessed, manual handling techniques. The CI and SC will have up to date manual handling qualifications and training in place.

Children will be accompanied during the walking measures to prevent any falls. The slope and stairs will be supplied with handrails. The slope is a disability access slope and conforms to Building Regulations Document M for dwellings. The stairs are a 4 stair set used in physiotherapy gyms within the NHS.

12.3 RISK Level

• Type A = A risk assessment has been completed, (please refer to the Risk assessment document titled 'RAINCOAT study risk assessment_23_06_22_v2'). This suggest that the study is of 'Low Risk' category and the appropriate steps will be taken to mitigate any potential risks posed to participants and no further action is required.

13. ADVERSE EVENTS

13.1 Recording and reporting of AEs

An adverse event (AE) is defined as any unfavourable and unintended sign that develops or worsens during the period of the trial, whether or not it is considered to be related to the trial. The risks of taking part in this trial have been assessed to be low.

Any new or worsening problems, which participants perceive to be related to participation in the study and occur at the single visit and within the following 48 hrs will be captured.

Examples of AEs that require reporting include:

- Aches and pains in the leg muscles following the study, lasting over 1 hour or requiring pain relief
- Injury related to the study procedure
- Fatigue following the procedure lasting more than 1 day
- Red marks or a reaction on the surface of the skin because of contact with the Biodex or Promove straps, which last for more than 10 minutes after the study is complete.

Participant's parent and or guardian will be asked to report any AE's that occur following the study assessment to the CI/ SC. Recorded AEs and SAEs will be presented at a Study management Group (SMG) meeting for review. The SMG will refer concerns to the Study Steering committee (SSC) for further review if required. AEs considered related to study participation will be followed until resolution or the event is considered stable. If the AE

occurs during the study procedure the Study Co-ordinator (SC) in discussion with the participant parents/Guardian will take responsibility as to whether or not an AE is of sufficient severity to withdraw the participant from the study. The participant may also voluntarily stop participating in the study if he or she perceives an incident to be an intolerable AE.

13.2 Recording and reporting of SAEs

Participants and the SC will be asked to report any SAEs directly to the chief investigator as soon as possible via e-mail / Telephone call. A serious adverse event (SAE) is defined as an untoward occurrence that:

(a) results in death;

(b) is life-threatening;

(c) requires hospitalisation (where hospitalisation is any admission leading to an overnight inpatient stay, or any day case appointment, or any ED attendance) or prolongation of existing hospitalisation;

(d) results in persistent or significant disability or incapacity;

(e) consists of a congenital anomaly or birth defect; or

(f) Is otherwise considered medically significant by the investigator.

SAEs will be recorded on the until the date the participant completes follow-up or withdraws from the study. SAEs may be volunteered by the participant or discovered by the SC through questioning, physical examination or other investigation, or as a result of direct reporting (e.g. by telephone) by the participant, independent clinician or other informant. Participants will be asked to report any SAEs directly to the chief investigator as soon as possible via e-mail / Telephone call.

SAEs will be followed until resolution/stable condition is reached. It is not anticipated that there will be any SAEs related to this cross-sectional observational study. Any SAE will be reported within 24 hours of the research team becoming aware of it. Any Unexpected Serious Related Events will be reported to REC within 15 days of CI being informed.

13.3 Responsibilities

Study Co-ordinator (SC):

- Checking for AEs when participant attends study day.
- Ensuring that all SAEs are recorded and reported to the sponsor and CI within 24hrs of becoming aware of the event and provide further follow-up information as soon as available.

- Completion of the SAE form must include the PI's assessment of causality i.e. whether there is a reasonable causal relationship between the SAE and attending the study appointment. If incomplete information is available at the time of reporting, all appropriate information relating to the SAE should be forwarded to the CI as soon as possible.

Chief Investigator (CI) / delegate or independent clinical reviewer:

- Clinical oversight of the safety of patients participating in the study, including an ongoing review of the risk / benefit.
- Ensuring that SAEs are sent to the sponsor within 1 working days of initial reporting. Using medical judgement in assigning the SAEs seriousness, causality and whether the event was anticipated where it has not been possible to obtain local medical assessment.
- Review of specific SAEs in accordance with the trial risk assessment and protocol.
- Central data collection and verification of AEs, SAEs, according to the study protocol onto study database.

14. MONITORING, AUDIT & INSPECTION

The research team will devise a monitoring plan specific to the study, based upon an initial pre-trial risk assessment, which will be updated as required throughout the study. The monitoring plan will include both central monitoring strategies and site set up reviews as appropriate and will be regularly reviewed. Monitoring will include oversight of processes relating to the safety of participants and the integrity/reliability of the study data, including adverse events reporting, participant enrolment, consent, eligibility, and adherence to study protocol and policies to promote the accuracy, and timeliness of data collection.
All study procedures will be conducted in accordance with the protocol and according to the principles of GCP.

15. ETHICAL AND REGULATORY CONSIDERATIONS

15.1 Research Ethics Committee (REC) review & reports

The study will not be initiated before the protocol, informed consent forms, Participation Information Sheets and other relevant documents (e.g. GP information letters, exit questionnaire and invites to participate) have received approval from the REC, HRA and the respective NHS R&D departments.

Should a protocol amendment be made that requires REC approval, the changes in the protocol will not be instituted until the amendment and revised informed study documents (if appropriate) have been reviewed and received approval from the REC and R&D departments. A protocol amendment intended to eliminate an apparent immediate hazard to participants may be implemented immediately providing that the REC are notified as soon as possible and an approval is requested. Minor protocol amendments only for

logistical or administrative changes may be implemented immediately; and the REC will be informed.

The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, 1996; the principles of ICH Good Clinical Practice, and the UK Policy Framework for Health and Social Care Research v3.3 07/11/17. All correspondence with the REC will be retained in the Study Master File/Investigator Site File

An annual progress report will be submitted to the REC within 30 days of the anniversary date on which the original favourable opinion was given, and annually until the trial is declared, ended. If the study is ended prematurely, the Chief Investigator will notify the REC, including the reasons for the premature termination. Within one year after the end of the study, the Chief Investigator will submit a final report with the results, including any publications/abstracts, to the REC and HRA.

15.2 Peer review

This protocol has been reviewed by a team of independent clinicians and clinical academics as part a successful application to Torbay Medical Research Fund.

15.3 Public and Patient Involvement

- Design of the research- Families have been consulted on the design of the study especially the everyday walking task.
- The protocol, adverts and patient information sheets have been reviewed by an expert parent and a teenager and altered to make the information more accessible to families and young people.
- Dissemination of findings- The patient representative will advise on appropriate dissemination of the results to reach families in the most accessible way.
- Payment for PPI will be in line with the INVOLVE guidance.

15.4 Regulatory Compliance

Before any site can enrol patients onto the study, the CI will apply for NHS permission from the site's Research & Development (R&D) department.
For any amendment that will potentially affect a site's NHS permission, the Chief Investigator/ Study Co-ordinator or designee will confirm with that site's R&D department that NHS permission is ongoing (note that both substantial amendments, and amendments considered to be non-substantial for the purposes of REC may still need to be notified to NHS R&D).

15.5 Protocol compliance

Planned protocol deviations, non-compliances, or breaches which are departures from the approved protocol are not allowed under the UK regulations on Clinical Trials and will not be used e.g. subjects will only be enrolled if they meet the eligibility criteria.
Accidental protocol deviations will be documented on the relevant forms and reported to the Chief Investigator immediately.

15.6 Notification of Serious Breaches to GCP and/or the protocol

The sponsor will be notified immediately of any case in which any of the following are compromised during the study conduct phase:
a) The safety or physical or mental integrity of the study participants
b) The scientific value of the study
c) The conditions and principles of GCP in connection with the study
The sponsor will be notified within 7 days of becoming aware of any accidental breach / amendment to the study protocol. The sponsor will be required to adjudge amendments prior to submitting these to REC/HRA.

15.7 Data protection and patient confidentiality

All investigators and study site staff will comply with the requirements of the Data Protection Act 1998 and General Data Protection Regulations (2018) concerning the collection, storage, processing, and disclosure of personal information and will uphold the Act's core principles.

- Data will be collected on the CRF, kept secure in a locked filing cabinet in the Research office of the CI.
- The participant's data will be stored using a unique participant identifier
- The participant's personal data and identification key will be stored on the secure study database. This will be stored for the duration of the study to allow contact with the participants (e.g. to clarify missing data and/or send study summaries). After this personal data will be destroyed.
- Electronic trial records will be stored in a secure encrypted, password protected database
- Only the research team will have access to the data
- The number of individuals necessary for quality control, audit, and analysis will be kept to a minimum.
- The confidentiality of data will be preserved when the data are transmitted to a co-investigator
- The CI is the data custodian for the duration of the study. Once the study is completed, the CI is responsible for the long-term storage of data in accordance with University of Plymouth regulations.

15.8 Financial and other competing interests

There are no financial or competing interests for the CI, TC at each site and committee members for the overall trial management.

15.9 Indemnity

University of Plymouth indemnity scheme will meet the potential legal liability of the sponsor(s):
·For harm to participants arising from the management of the research
·For harm to participants arising from the design of the research
· From harm arising to participants in the conduct of the research

This is a University of Plymouth research study. If an individual suffers negligent harm because of participating in the study, the University of Plymouth indemnity scheme covers University employers.

15.10 Amendments

Any amendments of the protocol will be submitted to the Sponsor, HRA, and REC for approval. Amendments will not be implemented until the REC/HRA grants a favourable opinion. All correspondence with the REC and HRA will be retained in the Study Master File and Investigator Site Files.

15.11 Post Study care

Where the SC identifies that treatment is required beyond the study appointment, the SC will liaise with their local therapy provider / GP to ensure that the patient is able to access care.

16. DISSEMINATION POLICY

- The data arising from the trial will be owned by the University of Plymouth research team
- On completion of the trial, the data will be analysed and tabulated and a Final Study Report prepared
- Study findings will be published in peer reviewed academic journals and presented at National and International conferences.
- TMRF funding will be acknowledged within the publications
- Participants will be notified of the outcome of the trial using a lay summary that will be sent via post or e-mail in accordance with participant preference.
- If a participant specifically requests results from the CI this information would be provided after the results had been published
- It is hoped that the anonymised participant level data set will be made available 1 year after the end of the trial via the Rehabilitation Research Group (University of Plymouth) website

16.1 Authorship eligibility guidelines and any intended use of professional writers

The CI and SC will have authorship on the final trial report

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18 APPENDICES

18.1 Appendix 1 – Authorisation and Participating sites

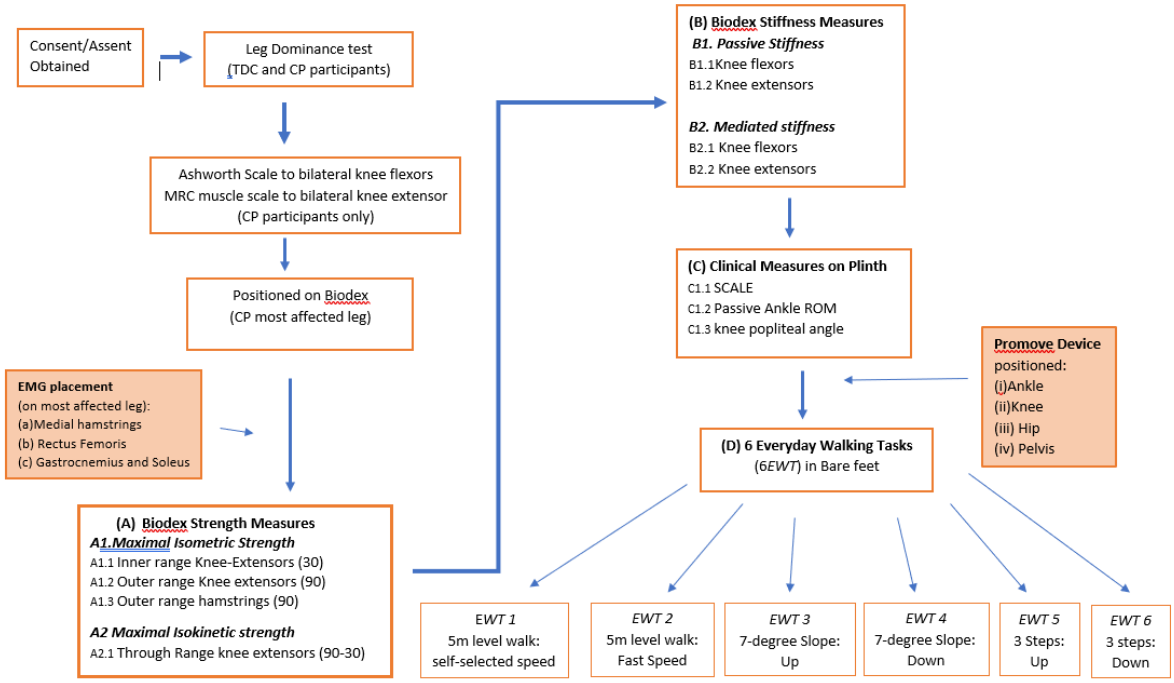
These will be attached following ethical/ R and D approval

18.1.1 Local documentation required prior to initiating a participating site.

To be inserted into the Trial Master File and each site file by the CI once these have been gathered:

- CVs of the research team
- GCP certification of the research team
- Site Specific Approval Site Specific
- R and D Approval

18.2 Appendix 2 –Protocol Flow Diagram



18.3 Appendix 3 – Safety reporting Flow Chart