**TRIAL PROTOCOL**

**A Multi-Centre Feasibility Randomised Control Trial of a Physiotherapy Programme using an Interactive Exercise Equipment to Improve Balance in Ambulant Children with Cerebral Palsy**

**Ability and quality of life for Children with CErebral Palsy Trial (ACCEPT study)**

Version: 1.0

Date: 10/01/2020

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

**RESEARCH REFERENCE NUMBERS**

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| **ISRCTN Number / Clinical trials.gov Number:** | Accepted registers include: * EU Clinical Trials Register (https://www.clinicaltrialsregister.eu). This register is linked to the EudraCT register, which is mandatory for all CTIMPs in patients authorised on or after 1 May 2004.
* International Standard Randomised Controlled Trials Number (ISRCTN) Register. This register accepts registration of randomised controlled trials and any other research study designed to assess the efficacy of health interventions in the human population.
* ClinicalTrials.gov. this is a register of studies in the United States and around the world.
 |
| **SPONSORS Number:** | N/A |
| **FUNDERS Number:** | **NIHR ref. ICA-CDRF-2017-03-041** |

# 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 publically 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: | Sarah Jones |  |
| Position:  | University Sponsor Representative |  |
|  |
| Signature:  |  | Date: 10/01/2020 |
| Name: | Rachel Rapson |  |
| Position: | Chief Investigator |  |
| Signature: |  | Date: 10/01/2020 |
| Name: | Kara Stevens |  |
| Position:  | Trial Statistician  |  |

# KEY TRIAL CONTACTS

|  |  |
| --- | --- |
| Chief Investigator | Rachel RapsonPeninsula Allied Health CentreUniversity of Plymouth PL6 8BHrachel.rapson@plymouth.ac.uk01752 58748607870501834 |
| Trial Co-ordinator | Jonathan MarsdenPeninsula Allied Health CentreUniversity of Plymouth PL6 8BHJonathan.marsden@plymouth.ac.uk01752 587590 |
| Sponsor | Sarah.C.JonesUniversity Sponsor RepresentativeResearch and innovationDrake CircusPlymouthPL6 8AAPlymouth.sponsor@plymouth.ac.uk |
| Funder(s) | National Institute of Health Research |
| Clinical Trials Unit | Wendy IngramClinical Trials ManagerPeninsula Clinical Trials UnitUniversity of PlymouthWendy.ingram@plymouth.ac.uk01752315252 |
| Data Manager | Laura CockingSenior Data ManagerPeninsula Clinical Trials UnitUniversity of Plymouth |
| Trial Statistician | Kara StevensResearch Fellow in Medical Statistics, University of Plymouth Kara.stevens@plymouth.ac.uk |

# LIST of CONTENTS

Contents

[SIGNATURE PAGE 3](#_Toc29199835)

[KEY TRIAL CONTACTS 5](#_Toc29199836)

[i. LIST of CONTENTS 6](#_Toc29199837)

[ii. LIST OF ABBREVIATIONS 11](#_Toc29199838)

[iii. TRIAL SUMMARY 13](#_Toc29199839)

[iv. FUNDING AND SUPPORT IN KIND 14](#_Toc29199840)

[v. ROLE OF TRIAL SPONSOR AND FUNDER 14](#_Toc29199841)

[vi. ROLES AND RESPONSIBILITIES 14](#_Toc29199842)

[Trial Management Committees 14](#_Toc29199843)

[Protocol Contributors 15](#_Toc29199844)

[vii. KEY WORDS 16](#_Toc29199845)

[1 BACKGROUND 17](#_Toc29199846)

[2 RATIONALE 18](#_Toc29199847)

[3 OBJECTIVES 19](#_Toc29199848)

[4 TRIAL DESIGN 20](#_Toc29199849)

[5 TRIAL SETTING 22](#_Toc29199850)

[6 PARTICIPANT ELIGIBILITY CRITERIA 22](#_Toc29199851)

[6.1 Inclusion criteria 22](#_Toc29199852)

[6.2 Exclusion criteria 22](#_Toc29199853)

[7 TRIAL PROCEDURES 23](#_Toc29199854)

[7.1 Site set up 23](#_Toc29199855)

[8 TRIAL INTERVENTIONS 23](#_Toc29199856)

[8.1 Intervention 23](#_Toc29199857)

[8.2 Usual Care 24](#_Toc29199858)

[8.3 Fidelity Testing 24](#_Toc29199859)

[9 RECRUITMENT 24](#_Toc29199860)

[9.1 Participant identification and approach 25](#_Toc29199861)

[9.2 Screening 26](#_Toc29199862)

[9.3 Payment 26](#_Toc29199863)

[9.3 Consent 26](#_Toc29199864)

[10 BLINDING 28](#_Toc29199865)

[10.1 Emergency Un-blinding 28](#_Toc29199866)

[11 RANDOMISATION 28](#_Toc29199867)

[11.1 Method of implementing the randomisation/allocation sequence 29](#_Toc29199868)

[12 DATA COLLECTION 29](#_Toc29199869)

[12.1 Baseline data 29](#_Toc29199870)

[12.3 Potential clinical outcome measures 29](#_Toc29199871)

[12.3.1 Potential Primary outcome measures: 29](#_Toc29199872)

[12.3.2 Potential secondary outcome measures: 30](#_Toc29199873)

[12.2 Feasibility Outcomes 30](#_Toc29199874)

[12.4 Qualitative assessments 31](#_Toc29199875)

[12.5 Withdrawal criteria 31](#_Toc29199876)

[13 DATA MANAGEMENT 32](#_Toc29199877)

[13.1 Data collection tools and source document identification 32](#_Toc29199878)

[13.2 Participant numbering 32](#_Toc29199879)

[13.2 Data handling and record keeping 32](#_Toc29199880)

[13.3 Archiving 33](#_Toc29199881)

[13.4 Access to Data 33](#_Toc29199882)

[14 NESTED QUALITATIVE STUDY 34](#_Toc29199883)

[14.1 Overview of the study 34](#_Toc29199884)

[14.2 Aims of Qualitative study 35](#_Toc29199885)

[14.3 Objectives of Qualitative study 35](#_Toc29199886)

[14.4 Study Design 35](#_Toc29199887)

[14.5 Recruitment 36](#_Toc29199888)

[14.6 Data collection 37](#_Toc29199889)

[14.6.1 e-Diaries 37](#_Toc29199890)

[14.6.2 Photo-elicitation interviews with the children 37](#_Toc29199891)

[14.6.3 Interviews with study parents and parents who withdraw or decline to participate 38](#_Toc29199892)

[14.6.4 Individual interviews with physiotherapists 38](#_Toc29199893)

[14.6.5 Interview/focus group settings 39](#_Toc29199894)

[14.6.6 Data management of Interview Data 39](#_Toc29199895)

[14.7 Data Analysis 39](#_Toc29199896)

[14.7.1 Rigour and Credibility 40](#_Toc29199897)

[15 END OF TRIAL 40](#_Toc29199898)

[16 SAFETY AND MANAGEMENT OF RISK 40](#_Toc29199899)

[16.1 Participant safety 40](#_Toc29199900)

[16.2 Therapist Safety 41](#_Toc29199901)

[17 ADVERSE EVENTS 41](#_Toc29199902)

[17.1 Recording and reporting of AEs 41](#_Toc29199903)

[17.2 Recording and reporting of SAEs 42](#_Toc29199904)

[17.3 Responsibilities 43](#_Toc29199905)

[18 STATISTICS AND DATA ANALYSIS 44](#_Toc29199906)

[18.1 Sample size calculation 44](#_Toc29199907)

[18.1.1 Estimation of recruitment rate 44](#_Toc29199908)

[18.2 Analysis populations 45](#_Toc29199909)

[18.3 Interim analysis and criteria for the premature termination of the trial 45](#_Toc29199910)

[18.4 Quantitative Analysis Plan 45](#_Toc29199911)

[18.4.1 Participant Population 45](#_Toc29199912)

[18.4.2 Feasibility Analysis 45](#_Toc29199913)

[18.4.3 Potential primary and secondary outcome analysis 46](#_Toc29199914)

[18.4.4 Definitive Trial Sample Size Estimation 46](#_Toc29199915)

[18.6 Missing Data 46](#_Toc29199916)

[18.7 Triangulation of data and progression criteria 46](#_Toc29199917)

[19 MONITORING, AUDIT & INSPECTION 47](#_Toc29199918)

[20 ETHICAL AND REGULATORY CONSIDERATIONS 47](#_Toc29199919)

[20.1 Research Ethics Committee (REC) review & reports 47](#_Toc29199920)

[20.2 Peer review 48](#_Toc29199921)

[20.3 Public and Patient Involvement 48](#_Toc29199922)

[20.4 Regulatory Compliance 48](#_Toc29199923)

[20.5 Protocol compliance 48](#_Toc29199924)

[20.6 Notification of Serious Breaches to GCP and/or the protocol 49](#_Toc29199925)

[20.7 Data protection and patient confidentiality 49](#_Toc29199926)

[20.8 Financial and other competing interests 50](#_Toc29199927)

[20.9 Indemnity 50](#_Toc29199928)

[20.10 Amendments 50](#_Toc29199929)

[20.11 Post trial care 50](#_Toc29199930)

[21 DISSEMINIATION POLICY 50](#_Toc29199931)

[21.1 Dissemination policy 50](#_Toc29199932)

[21.2 Authorship eligibility guidelines and any intended use of professional writers 51](#_Toc29199933)

[22 REFERENCES 52](#_Toc29199934)

[23 APPENDICIES 54](#_Toc29199935)

[23.1 Appendix 1 – Authorisation of participating sites 54](#_Toc29199936)

[23.1.1 Required documentation 54](#_Toc29199937)

[23.1.2 Procedure for initiating/opening a new site 54](#_Toc29199938)

[23.1.3 Principal Investigator responsibilities 54](#_Toc29199939)

[23.2 Appendix 2 – Schedule of Procedures 55](#_Toc29199940)

[23.3 Appendix 3 – Safety Reporting Flow Chart 56](#_Toc29199941)

[23.4 Appendix 4 – Amendment History 57](#_Toc29199942)

# LIST OF ABBREVIATIONS

Define all unusual or ‘technical’ terms related to the trial. Add or delete as appropriate to your trial. Maintain alphabetical order for ease of reference.

AE Adverse Event

CDC Child Development Centre

CI Chief Investigator

COPM Canadian Occupational Performance Measure

CP Cerebral Palsy

CRF Case Report Form

CTU Clinical Trials Unit

DMC Data Monitoring Committee

GCP Good Clinical Practice

GMFCS Gross Motor Function Classification System

ICF Informed Consent Form

ISRCTN International Standard Randomised Controlled Trials Number

NHS R&D National Health Service Research & Development

PBS Pediatric Balance Scale

PI Principal Investigator

PPI Patient and Public Involvement

PIC Participant Identification Centre

PIS Participant Information Sheet

QA Quality Assurance

RCT Randomised Control Trial

REC Research Ethics Committee

SAE Serious Adverse Event

SDV Source Data Verification

SOP Standard Operating Procedure

SSI Site Specific Information

TMF Trial Master File

TMG Trial Management Group

TSC Trial Steering Committee

# TRIAL SUMMARY

|  |  |
| --- | --- |
| Trial Title | A Multi-Centre Feasibility Randomised Control Trial of a Physiotherapy Programme using an Interactive Exercise Equipment to Improve Balance in Ambulant Children with Cerebral Palsy. |
| Internal ref. (or short title) | ACCEPT |
| Clinical Phase  | Feasibility |
| Trial Design | Mixed methods RCT |
| Trial Participants | Children with cerebral palsy aged 4-18 years |
| Planned Sample Size | 40 |
| Treatment duration | 10 weeks |
| Follow up duration | 20 weeks |
| Planned Trial Period | 1/5/2020 until 1/8/2022 |
|  | Objectives | Outcome Measures |
| 1 | To assess the feasibility of conducting an RCT evaluating the effect of interactive exercise equipment on walking for children with cerebral palsy | Feasibility OutcomesDescriptive statistics of planned outcome measures |
| 2 | To assess the feasibility of the intervention | Adherence, cost and safety of the intervention.Descriptive statistics |
| 3 | Investigate the participants’ views of participating in the study | Thematic analysis of semi structured interviews |

# FUNDING AND SUPPORT IN KIND

|  |  |
| --- | --- |
| **FUNDER(S)**(Names and contact details of ALL organisations providing funding and/or support in kind for this trial) | **FINANCIAL AND NON FINANCIAL SUPPORT GIVEN** |
| **National Institute of Health Research**ICA-CDRF-2017-03-041 | Financial support |
| **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 PenCTU by way of formal agreement.

The National Institute funds this study for Health Research as part of a Clinical Doctoral Fellowship for Rachel Rapson ref. ICA-CDRF-2017-03-041. The role of the funder is to provide feedback from the NIHR funding panel and 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

## Trial Management Committees

Trial Management Group

The trial management groupTMG will consist of R Rapson’s supervisory team Prof Jos Latour, Prof Bernie Carter, Prof Jonathan Marsden, Rachel Rapson, CTU Trial Manager (Dr Wendy Ingram), CTU Data Manager (Laura Cocking) and trial statistician (Dr Kara Stevens).

Frequency of Meetings:

The TMG will meet approximately on a monthly basis (via teleconferencing / skype or face to face)

Responsibilities: The role of this group is to oversee the general management of the day-to-day running of this trial. The responsibility of this group is to ensure all practical details of the trial are progressing and working well and everyone within the trial understands them. This will include, for instance, monitoring adverse events, recruitment and attrition rates, the project timeline and finances. It will also include responsibility for the release of the trial results.

* Trial Steering Committee

The trial steering committee (TSC) will consist of an independent chairperson (Prof Stuart Logan), independent statistician (Trish Hepburn), PPI representatives (Helen Hobbs, Alex Hobbs), and sponsors representative (Sarah Jones), Local R&D Manager (Dr Fiona Roberts). The trial statistician, CTU trial manager(s) and Sponsor representative will be invited to meetings as observers.

Terms of reference for the TSC will be agreed before the start of the study and incorporated into a TSC Charter, updated from time to time as required.

The TSC will oversee progress with, and associated processes for:

* Participant enrolment, consent, eligibility, and allocation to trial groups
* Adherence to trial interventions and policies to protect participants, accuracy, and timeliness of data collection
* Potential primary and feasibility outcome data completeness
* Adverse events

Monitoring will be conducted across the recruitment site for enrolment rates, and atypical (low or high) numbers of reported adverse events, withdrawals or decline

## Protocol Contributors

**Rachel Rapson** is the CI and Doctoral Research Fellow, and has overall responsibility for the implementation of this trial. She has the responsibility for preparing the protocol, writing and submitting the ethics and HRA applications, developing training packages, preparing periodic reports, recruitment, and clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk and/or benefits. She will also take the lead on data analysis and article publication. She is the TMG chair and a TSC member. She is an experienced Physiotherapy Clinical manager undertaking doctoral-level study while employed by the NHS and the University of Plymouth.

**Jonathan Marsden** is Professor of Rehabilitation University of Plymouth. He will act as co-investigator. He will be first supervisor for the part-time PhD studies of the Rachel Rapson and will provide guidance on the protocol; management of the study, data collection and analysis and write up and dissemination.

**Jos Latour** isProfessor of Nursing, University of Plymouth. He will act as a co-investigator to the trial and overall as a second supervisor for the part-time PhD studies of Rachel Rapson. He will also provide guidance on the protocol; management of the study, data collection and analysis and write up and dissemination.

**Bernie Carter** is Professor of Children’s Nursing, Edge Hill University. She will act as a co-investigator to the trial and overall as a third supervisor for the part-time PhD studies of Rachel Rapson. She will also provide guidance on the protocol; management of the study, data collection and analysis (with a particular focus on the qualitative data), write up and dissemination.

**Wendy Ingram** is theClinical Trials Manager at Peninsula Clinical Trials Unit (University of Plymouth). She will lead the CTU input to the study and provide mentorship to the CI and is a TMG member and TSC observer.

**Kara Stevens** will assist with the development of the protocol and be responsible for supervising and mentoring the CI on statistical analyses. She is a TMG member and TSC observer.

**Laura Cocking** is a senior Data Manger at the Peninsula Clinical Trials Unit (University of Plymouth). She provides guidance on the protocol and provides mentorship on data management during the trial.

# KEY WORDS

Cerebral Palsy, Physiotherapy, Balance, Quality of Life, Gaming

# 1 BACKGROUND

Cerebral palsy (CP) is a group of permanent disorders affecting the development of movement and posture that occurs in two to four per 1000 children [1]. Difficulties with walking and balance are common and can limit participation in schooling and functional activities [2-5]. Children with CP, for example, only spend 3.4 hours per week engaging in physical activity, nearly half that seen in typically developing children [6].

Walking ability can be classified using the Gross Motor Function Classification system (GMFCS) [7]. Children with GMFCS classification I-II are able to walk functionally outdoors, while children with grade III GMFCS require walking aids. Children with GMFCS I-III, the focus of the proposed study, comprise around 67% of the population (about 23,400) of children with CP in the UK [8].

There are multiple causes of walking difficulties in children with CP, including muscle weakness, contracture or bony deformity. Spasticity and weakness affect 80% of ambulant children with CP [9]. Secondary musculoskeletal problems develop throughout childhood due to the effect of spasticity on muscle length. Muscle growth does not keep pace with bone growth and this leads to deformity of the developing skeleton [10]. Children with CP often have poor balance, which further impacts on walking ability and everyday function [11].

Children with CP frequently undertake daily exercise programmes aimed at maintaining range of movement, strengthening weak muscles and developing balance skills. In Patient and Public Involvement (PPI) consultations, some children have reported that they do not want to do their therapy at home, feeling that it is boring or that it limits their participation in other activities. Parents reported that having to act as the therapist, facilitating their child to do stretches or training, conflicts with the parental comforting and protector role. Therefore, it is desirable to find exercise activities that are both fun and therapeutic which the child can do as independently as possible.

Current usual care consists of factors such as stretching, progressive strengthening exercises and functional task-related training. In many cases, children with CP find it hard to undertake exercises in functional positions such as standing, without support from a carer. The Happy Rehab™ (Innovaid, Denmark) interactive gaming trainer was developed (see figure 1) and marketed to help children exercise independently in a functional supported standing position. The novel interactive trainer provides support around the hips and additional assistance via servomotors aligned to the ankle and knees. This allows the child to exercise muscles functionally in novel ranges, e.g. strengthening the thigh muscles with the hip and knee in a straighter position. Children play a series of tailored exercise games controlled by the child’s leg movement. The games-based exercises increase motivation and require the child to control the games by moving their weight side-to-side, forward and backward. It is proposed that this may improve balance during dynamic tasks such as walking.

  

**Figure 1-The interactive exercise equipment**

Whilst the interactive trainer is used more readily in Scandinavian countries and there is growing interest in the UK, there is limited evidence as to its effectiveness. A small scale study of the interactive trainer that found marked improvements in walking, had a number of limitations in terms of outcome measures used, lack of follow up or control group [12]. Therefore, evidence is still required to establish the efficacy of the equipment.

# 2 RATIONALE

Before a full trial can be conducted to establish the effectiveness of the Happy Rehab™ interactive gaming trainer, there are still some questions with regards to the feasibility of the trial, intervention and conduct of the trial which need to be resolved.

In PPI consultations, children and families have expressed a desire to use the trainer at home in place of their usual care. Elsewhere, stakeholders have expressed the view that the interactive trainer would be more efficiently used in a clinical base to enable multiple users to train on the equipment. Physiotherapists have described the ability to support intensive training in a clinic as potentially challenging to staff. However, there are some clinical bases in special schools, which may allow the ease of access to multiple users. Therefore, as part of the feasibility study, the location of the trainer may be clinic, home or school based in order to compare the intensity of training in different settings, clinicians, parents and children’s views on training, as well as treatment costs and the durability of the equipment or ease of arranging repairs.

In order to measure dynamic balance we have devised and established the validity and reliability of a simple stepping test in children with CP and typically developing children (Rapson, Marsden, Pitsouni un-published work 2019). However, as this is a new measurement the necessary information to produce a power calculation is not currently available.

This study aims to establish whether it is feasible to conduct an RCT to assess the effectiveness of using an interactive trainer in children with CP. Children will be randomised to either a ten-week programme of intensive training with the Happy Rehab™ device in either a CDC, school or home setting, or to the control group of usual physiotherapy care. It will explore the feasibility and acceptability of the intervention, participants’ views on randomisation, likely recruitment and retention rates and the frequency of any adverse events. The study will assess the feasibility of the proposed outcome measures, in terms of user satisfaction, percentage completed and ability to detect. Standard deviation confidence intervals, together with previous literature, will inform power calculations for the main RCT.

# 3 OBJECTIVES

1) Determine the feasibility of a definitive trial by assessing:

* Recruitment rate
* Retention rates
* Effectiveness and acceptability of randomisation
* Change in clinical outcome measures
* Effectiveness of concealment of allocation up to week 10
* Concurrence with other surgical and medical interventions
* Fidelity to treatment protocol
* Appropriateness of clinical outcome measures
* Sample size estimate for definitive trial

2) Determine the acceptability of the intervention by assessing:

* Adherence to treatment
* Safety of intervention
* Cost of intervention and support needed to use it

3) Explore the views of a sub group of the study participants

By interviewing children, parents and physiotherapists about their experiences of participating in this feasibility RCT to assess the acceptability of the trial and the intervention.

# 4 TRIAL DESIGN

The trial is a single-blinded; mixed-methods feasibility randomised controlled trial. Participants will be randomly allocated 1:1 to either usual care or Happy Rehab™ interactive trainer. A sub group of participants will be interviewed about to find their experiences of taking part. The research question can be framed in the following way:

P Population – Children with cerebral palsy aged 4-18 years

 I Intervention – A programme of physiotherapy using the interactive training equipment

 C Comparison group – Usual care

 O Outcome of interest – Feasibility of the trial and intervention

 T Time – Three times per week for 10 weeks training plus 10 week follow up

The trial flow chart can be seen in figure 2.



# 5 TRIAL SETTING

* A multi-centre trial based in the Child Development Centres (CDCs) and the community settings, to which they deliver services e.g. school or home. The CDCs provider organisations are Royal Cornwall Hospitals Trust, University Hospitals Plymouth NHS Trust, Torbay and South Devon NHS Trust, North Devon NHS Trust, Royal Devon and Exeter NHS Foundation Trust as well as Vranch House Charity.
* Community paediatric physiotherapists will recruit children from their caseloads.
* The intervention will take place in either the child’s home, school or the local physiotherapy clinic.
* The child’s treating physiotherapist will set up the intervention. The child will be helped to access the equipment and their training supervised by the child’s therapist, teaching assistant or their parent.
* The qualitative interviews will take place in the child’s home or CDC.

# 6 PARTICIPANT ELIGIBILITY CRITERIA

## 6.1 Inclusion criteria

1. Diagnosis of CP GMFCS I-III.
2. Aged 4-18 years.
3. Leg weakness (≤4/5 on the MRC muscle strength rating scale) in at least 1 muscle group
4. Leg hypertonia (≥1 on the Tardieu scale fast stretch) in at least 1 muscle group
5. Ability to interact with a computer game using a mouse or joystick.

The age range reflects the recommended age range for the interactive exercise. Other inclusion criteria reflect the need to show an impairment in leg strength and tone, core features of a spastic Cerebral Palsy presentation.

## 6.2 Exclusion criteria

1. Selective dorsal rhizotomy or Multi level orthopaedic surgery within the last 12 months
2. Soft tissue surgery in lower limbs in last 6 months.
3. Anti-spasticity botulinum toxin injections within previous 3 months.
4. Training with the Happy Rehab™ in the last 4 months.

The exclusion criteria include interventions that could still produce a clinical effect during the trial training period. Children will not be excluded if, after recruitment into the trial, they undertake operative procedures and/or receive botulinum injection.

# 7 TRIAL PROCEDURES

## 7.1 Site set up

Recruitment will take place sequentially in each CDC area in order to ensure that the limited number of training devices are issued in the most efficient way.

In preparation for recruitment, the CI will visit each site to familiarise physiotherapists with the eligibility criteria and trial procedures. The trial coordinator will arrange delivery of the training device to the CDC and the CI will demonstrate how to use it. The CI will teach the physiotherapists how to set up the trainer in order to meet the child’s needs and to select and use the menu of games. The CI will train the physiotherapists to use the SOPs and to teach and disseminate the SOP to carers.

# 8 TRIAL INTERVENTIONS

## 8.1 Intervention

The Happy Rehab™ interactive trainer involves a standing frame device incorporating servomotors and a games system (Figure 2). Four frames will be available and situated in special schools, child development centres or the child’s home. The child’s physiotherapist will be trained to set up the device targeting exercises to improve range of movement, contracture and muscle weakness. This may include active-assisted hip, knee or ankle movements within specified ranges of movement or side-to-side and forward and back weight transfer. The treating physiotherapist will personalise the exercise programme based upon a standardised assessment, including a discussion with the child and their guardian about their goals and aims of any intervention.

The child will use a pseudonym of their choice to log onto the games, and to maintain confidentiality. The games will be played within the mid-range of muscle length to begin with so that the games are difficult but achievable. This will aid motivation and adherence. After five weeks, the child’s physiotherapist will progress the games by requiring the muscles to work in the inner and outer ranges of movement and/or against increased resistance. Training will build up to 20 minutes per day, 3 days a week over a 2-week period, with progression to a 30-minute programme per day, 3 days a week after five weeks. All children will follow a series of games following a 5-minute warm up of continuous passive movement.

Collaborative goal setting combined with a paper diary will allow the child/guardian to monitor progress over time and record their satisfaction with their exercise programme. This will be used to aid motivation in the intervention group. The interactive trainer records the training session (duration, games performed games outcomes) to provide a description of the parameters of training.

## 8.2 Usual Care

The control group will receive a home programme individualised for each child. This will be a mixture of active stretches and balance exercises lasting 20-30 minutes. The content of the home programme will be documented and participants will complete a diary indicating the type and number of exercises performed. The participants in the control group will receive the same goal setting as the intervention group.

## 8.3 Fidelity Testing

Physiotherapists will be trained at the outset of the study to include training about the intervention. Fidelity will be assessed through diaries of exercise use and recording of exercise parameters via the interactive trainer. Additionally, members of the research team will observe exercise sessions and complete a fidelity checklist (n=10 participants) to ensure the intervention follows protocol.

# 9 RECRUITMENT

The recruitment flow diagram in figure 3 shows the process by which potential participants are identified, screened and recruited.



## 9.1 Participant identification and approach

Recruitment will occur through the Clinical Research Network and clinical teams at five NHS Trusts: Royal Cornwall Hospitals Trust, University Hospitals Plymouth NHS Trust, Torbay and South Devon NHS Trust, North Devon NHS Trust, Royal Devon and Exeter NHS Foundation Trust as well as Vranch House Charity.

Participants will also be recruited via adverts in newsletters of groups such as PenCRU, Cerebra, Contact-a-Family; British Academies for Community Child Health and for Childhood Disease and British Academy Childhood Disability.

* Physiotherapists, occupational therapists, pediatricians and orthopedic surgeons will identify potential participants during clinics and via their caseload lists. Clinicians may approach children on caseloads by telephone before sending out an information pack to those who are interested in taking part.
* Posters and fliers will be produced for clinicians to distribute to potential participants. Adverts will be used to raise awareness of the study and will be placed in clinics where children with CP might have appointments and shared on the ACCEPT study Facebook and Twitter pages.
* The CI will confirm eligibility for potential participants responding to adverts; this will involve giving consent for the CI to check medical records to see if the child meets eligibility criteria.

Separate participant information sheets will be available for parents, young adults (16-18 years) and easy read versions will be available for children. Consent forms will be provided to parents and, young adults, and assent forms provided to children. Participants / guardians will have at least 24 hours after provision of the information sheet to discuss the trial with the research team.

## 9.2 Screening

The local PI will use a trial-specific screening log to record numbers of children eligible, ineligible and the numbers of children approached and numbers of study information packs given out at each site.

Potential participants who respond to the invitation will be screened for suitability using a telephone questionnaire to check diagnosis, age, GMFCS level and ability to play a game using a mouse or joystick.

## 9.3 Payment

Travel expenses (up to £25/visit) will be reimbursed for all assessment sessions.

## 9.3 Consent

The informed consent process will involve:

* Discussion between the potential participant and his/her legally guardian and a member of the research team/designated individual. about the nature and objectives of the trial and possible risks associated with their participation
* Presentation of written material (e.g. Participant information leaflet and informed consent form
* The opportunity for potential participants and parents/guardians to ask questions
* Assessment of capacity for parents or young adults. For consent to be ethical and valid in law, participants must be capable of giving consent for themselves. The Clinical Trial Regulations define a child as a person under the age of 16 years of age. Practice for young people and children this means that only medicinal products which are likely to be of significant value for young people and children are fully studied and the protection of participating children is fully considered.

Written informed consent and assent will be recorded prior to the child and parent undertaking the first baseline measurement session (T0).

Families will also be invited to take part in the nested qualitative study. Following purposive sampling, eligible families will be approached for consent to be recruited to the qualitative study. People who do not wish to take part in the study or withdraw from the study will be invited to undertake a short (less than five minutes) telephone interview to help understand any barriers and facilitators to participating in the trial to aid in future recruitment. A separate information sheet will be available for the interviews that will emphasise that the aim is to aid in future study design and recruitment and not to influence the family’s decision in any way.

The CI will obtain informed written consent from the guardian and the assent of the child participating in the study. Capacity will be assessed. A person with capacity will:

* + understand the purpose and nature of the research
	+ understand what the research involves, its benefits (or lack of benefits), risks and burdens
	+ understand the alternatives to taking part
	+ Be able to retain the information long enough to make an effective decision.
	+ be able to make a free choice
	+ be capable of making this particular decision at the time it needs to be made (though their capacity may fluctuate, and they may be capable of making some decisions but not others depending on their complexity)
	+ where participants are capable of consenting for themselves but are particularly susceptible to coercion, it is important to explain how their interests will be protected

The CI will be authorised, trained and competent to consent patients according to the approved protocol, principles of ICH GCP. Consent with children will follow the legal framework and ethical considerations for involving young people (between the ages of 16 and 17) in research that are set out in the Department of Health Reference Guide to Consent for Examination or Treatment (2009).

The right of a participant to refuse participation without giving reasons will be respected. The participant will remain free to withdraw at any time from the trial without giving reasons and without prejudicing his/her further treatment.

The information sheet will contain a point of contact so that children and guardians are able to discuss or obtain further information about the trial. Permission will be gained via the consent form for data collected up to a point of withdrawal to be used in the study.

# 10 BLINDING

This will be a single blinded RCT. The CI will be blinded to allocation while carrying out the assessments at baseline and week 10.

During qualitative interviews at week 11, it will not be possible to for the CI to remain blinded to group allocation for the 12 participants taking part. However, the CI will remain blinded to group allocation for the remaining 28 of the participants for the follow up assessment at week 20.

## 10.1 Emergency Un-blinding

* The participant code and personal information for the trial are held on the PenCTU trial database
* In the event a code is required to be un-blinded a formal request for un-blinding will be made by the Investigator/treating health care professional

# 11 RANDOMISATION

Participants will be randomly allocated to one of two groups: one group will receive a physiotherapy programme using the interactive training equipment (Intervention) while the participants in the other group will receive usual care (Control).

The random allocation of groups will be minimised by age and by GMFCS level, with the aim of balancing the distribution of participants between allocated groups for those:

* age 9 or below Vs 10 years or above;
* GMFCS level I or II vs level III.

PenCTU will generate and implement the randomisation and minimisation sequence.

## 11.1 Method of implementing the randomisation/allocation sequence

The randomised allocations will be computer-generated by the CTU in conjunction with an independent statistician, in accordance with the CTU’s standard operating procedure. The randomisation list and the program used to generate the list will be stored in a secure network location within the CTU, accessible only to those responsible for provision of the randomisation system.

The blinded assessor will enter the details required for randomisation into the study website, book the participant’s first appointment with the treating therapist.

An email will be generated by the study website to inform the local treating therapist of the participant’s allocated group. The treating therapist will reveal group allocation to the participant at the first session.

The un-blinded researcher will arrange for the interactive trainer to be transported to the site where the child usually does their physiotherapy e.g. school, CDC, home.

# 12 DATA COLLECTION

## 12.1 Baseline data

* GMFCS level
* Date of birth
* Medical and surgical history
* Height, weight, pelvic depth
* Frequency and location of usual physiotherapy
* Other sports and social activities

## 12.3 Potential clinical outcome measures

The following assessments will be carried out at week 0, 10 and those indicated with \* at 20 weeks follow up. The physical assessments will take 70 minutes followed by up to 30 minutes goal setting using the COPM.

### 12.3.1 Potential Primary outcome measures:

* Next Step test of dynamic balance\* [13, 14]
* Pediatric Balance scale\* [15]

### 12.3.2 Potential secondary outcome measures:

* Walking kinematics\*
* Muscle strength of quadriceps, hamstrings, and gastrocnemius and hip abductors using a hand held dynamometer (three measurements)\*.
* Passive range of movement and modified Tardieu scale [16] of quadriceps, hamstrings, gastrocnemius and hip adductors using goniometer (three measurements)\*.
* COPM- Canadian Occupational Performance Measure [17]
* CHU-9D- Paediatric Quality of Life measure [18]

## 12.2 Feasibility Outcomes

To achieve the trial objectives outlined in section 3 the following outcome measures in Table 1 will be obtained.

**Table 1 ACCEPT Feasibility Outcomes**

|  |  |
| --- | --- |
| **Objective** | **Outcome** |
| 1. **Feasibility of Definitive Trial**
 |
| Acceptability of the trial and intervention  | Interviews of staff, parents and children |
| Can we recruit and retain participants? | Number of participants eligible Number recruited and randomised, date of recruitment recorded on study databaseRecruitment sourceNumber of withdrawals. Number of participants lost to follow-up.  |
| Effectiveness and acceptability of randomisation | Comparison of participant characteristics: severity, distribution of motor impairment, associated impairments at baselineInterviews |
| Effectiveness of concealment of allocation up to week 10 | Number of times CI correctly guessed treatment allocation |
| Concurrence with other surgical and medical interventions | Number of operations or procedures that target balance and walking during the intervention and follow up period. |
| Change in clinical outcome measures | Change in assessment scores of outcome measures  |
| Assess appropriateness of outcome measures | Number and percentage of outcome measures completed at each time pointInterviews |
| 1. **Feasibility of Intervention**
 |
| Adherence to treatment | Diary data frequency and duration of training |
| Acceptability of treatment intervention | Incidence of breakdown of equipmentNumber of times participants were unable to access equipmentParticipant view on acceptability of interventions by Interview  |
| Cost of intervention and support needed to use it | Local physiotherapist record of staff time and grade used to support intervention. Travel costs of staff and families.Number and cost of repairs |
| Safety of intervention | Number and type of SAE and AE  |
| 1. **Investigate the participants’ views of participating in the study**
 |
| Semi structured interviews | Thematic analysis of interviews and photos |

## 12.4 Qualitative assessments

Children and their parents, who are taking part in the qualitative study, will be interviewed at week 11 (see nested qualitative study 16.1).

## 12.5 Withdrawal criteria

Participants who withdraw will be invited to consent to a withdrawal interview. This will involve a short (less than five minutes) telephone interview to help understand any barriers and facilitators to participating in the trial to aid in future recruitment. A separate information sheet will be available for the interviews that will emphasise that the aim is to aid in future study design and recruitment and not to influence the family’s decision in any way. Outcome data from withdrawers will be included in the intention to treat analysis.

12.6 Economic evaluation

Resource use including key accessible cost data (e.g. therapist time; equipment costs) that can inform whether it is possible to collect a future health economic evaluation.

# 13 DATA MANAGEMENT

## 13.1 Data collection tools and source document identification

Trial data collected will be recorded on trial specific case report forms provided by the CTU. The Case Report Form (CRF) will be a printed paper document. Data captured in the CRF will be considered source data. The baseline data and outcome measures that will be recorded are outlined in section 12.2.

The blinded assessor will complete the CRFs for all participants. Completeness of data will be maximised by -

* Checking all forms at each assessment to ensure there are no missing items
* Wherever possible, arrange another assessment session, should the pre-scheduled session be cancelled/ not attended by the participants

The trial co-ordinator will prompt the participants to return their diaries, should they fail to do so within two weeks of the due date.

Once complete original CRFs will be signed and dated by a member of the trial site team before being sent by post to the CTU, in accordance with written instructions within the CRF. Pre-addressed, Freepost (prepaid) envelopes will be supplied for this purpose. A photocopy of each CRF will be kept in the site file.

13.2 Participant numbering

Each participant will be allocated a unique participant number when they are registered on the study database.

## 13.2 Data handling and record keeping

The CTU data management team is responsible for data management, including data entry of CRFs and questionnaires. Original CRF booklets will be posted to the CTU at agreed time points for double-data entry on to a SQL Server database using a bespoke, password-protected, website, designed and maintained by the CTU data programming team and hosted on a University of Plymouth server. Electronic study records will be held over the lifetime of the project in secure storage solution(s) which will always be aligned with the University of Plymouth information security classification policy.

All data collection forms will be tracked by the CTU using a web-based trial management system. Completed CRFs will be checked on receipt at CTU and any obvious errors or omissions rectified as far as possible by means of a formalised data query/clarification procedure.

Double-entered data will be compared for discrepancies using a stored procedure and discrepant data will be verified using the original paper data forms. Before database lock, a proportion of original paper records will be checked against the database to ensure accuracy of the final dataset.

Qualitative data in the form of interview recordings will be transcribed and anonymised by the CI or delegated staff as soon as practicable; original recordings will be held securely as an encrypted file on the University of Plymouth server, until completion of the qualitative data analysis process, then deleted.

Trial data will be analysed by Rachel Rapson (CI) with support from K Stevens (trial statistician).

13.3 Archiving

The CI will be responsible for archiving the original study data (paper and electronic formats) and essential documentation (contents of Trial Master File) in a secure location for a minimum period of 10 years after the end of the trial. Archiving will be authorised by the Sponsor following submission of the end of study report. Each individual study site will be responsible for archiving copies of local study data (as applicable where copies exist) and essential documentation (contents of Investigator Site File) in a secure location for the same period. No essential documents should be destroyed unless or until the Sponsor gives authorisation to do so.

## 13.4 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 trial will be available for inspection on request by the participating research team, University of Plymouth representatives, the REC, local R&D Departments and the regulatory authorities.

# 14 NESTED QUALITATIVE STUDY

## 14.1 Overview of the study

This embedded qualitative mixed methods (interviews, e-diary, photographs and focus groups) study will be conducted to understand the views of children, parents and physiotherapists on the trial. The process of this nested study are shown in the flow diagram (figure 4).

****

Data generation with the children will be undertaken using semi-structured interviews incorporating a photo-elicitation method. Twelve children in total drawn from the control group (n=6) and intervention group (n=6) and across the range of severities will be given electronic tablets and asked to record a diary and take 5-20 photos to represent their experiences of their exercise programme. This will then guide the discussion during the interview at the end of week 10. The interviews will explore their views on the trial as well as factors affecting adherence to exercise. Data generation via interviews with parents (n=12-24) of the 12 children and individual with physiotherapists (n=4) will be undertaken to explore their views on trial feasibility. Decliner and withdrawer interviews will be undertaken where possible. Data will be transcribed and analysed thematically using triangulation with the diary entries.

## 14.2 Aims of Qualitative study

This study has two main aims:

1. To explore the experiences of children, parents and physiotherapists of their participation in the feasibility study to inform the effective delivery of the main RCT.
2. To explore the reasons for parents declining to participate/withdrawing in the study.

## 14.3 Objectives of Qualitative study

• Investigate participants’ views on trial design (e.g. acceptability of recruitment and consent procedures) and data collection methods

• Explore participants’ experience of, and adherence to, the intervention.

• Explore physiotherapists’ experiences of taking part in the study, and acceptability of a future RCT.

• Identify reasons why parents of eligible patients decline to take part in or withdraw their child from the study

## 14.4 Study Design

This qualitative study uses novel ways of data collection with the children including semi-structured e-diaries using electronic tablet devices and photo-elicitation interviews. Semi-structured interviews will be undertaken with parents/carers and clinicians. Triangulation of the methods will be used to provide credibility, ensuring that the understanding of the full scope of the experiences related to participating in the trial is as complete as possible from the perspectives of the children, parents and physiotherapists.

Sampling: Purposive sampling via a sampling matrix will acquire a representative view of both groups (control versus intervention) and of different levels of motor impairment (GMFCS I/II versus III). Twelve parent-child dyads will be recruited (30% of the total sample of the feasibility study): 12 children and 12-24 parents, depending on whether one or both parents participate (six children-parent dyads from the control group and six children-parent dyads from the intervention group of the feasibility RCT).

In addition, four physiotherapists who have been involved in delivering the intervention will be purposively sampled: one who delivered the intervention in the home, one who delivered the intervention in a school or clinic, one each from an urban and a rural setting.

Sampling of up to eight parents who declined or withdrew their child from the study will be undertaken.

**Table 2 Purposive sampling matrix for qualitative interviews.**

|  |  |  |
| --- | --- | --- |
|  | Control | Intervention |
| Participating child and parent  | n=1 <11 yearsn=1 >11 yearsn=1 GMFCS IIIn=1 GMFCS I or IIn=1 schooln=1 home | n=1 <11 yearsn=1 >11 yearsn=1 GMFCS IIIn=1 GMFCS I or IIn=1 clinicn=1 home/school |
| Treating Physiotherapist |  | n=1 schooln=1 homen=1 ruraln=1 urban |
| Parent who declined for their child to participate or who withdrew their child | n=8 |

## 14.5 Recruitment

Children and parent dyads who have already been recruited to the feasibility RCT and specifically identified through the purposive sampling matrix will be contacted by the research team and invited to participate in this qualitative study before the intervention begins. The researcher will undertake the recruitment and qualitative assessment at the end of the 10-week intervention period.

Four physiotherapists will be invited from the nine teams of physiotherapists delivering the intervention.

Up to eight parents, who declined for their child to be randomised to or who withdraw from the study will be approached to try to find out the reasons for this and whether anything in the study design can be changed to limit attrition ahead of the main trial. This approach will be undertaken with particular sensitivity to ensure that parents do not feel that this approach is inappropriate. Parents will be recruited sequentially.

Specific informed consent/assent will be sought from parents (participating, declining/withdrawing), children and physiotherapists.

## 14.6 Data collection

In order to trigger children’s engagement in sharing their experiences child-oriented opportunities and approaches to generating data will be used [52]. Rather than relying solely on verbal approaches, the triggers for child engagement include the use of electronic tablet devices to encourage digital recording of experiences using a format that is a familiar part of their everyday lives. In addition, the use of photographs within the photo-elicitation interviews provides an additional visual trigger for engagement. The researcher will make field notes, recording thoughts and observations made during the process of data collection.

### 14.6.1 e-Diaries

The e-diary will enable the child to record on a daily basis their thoughts and feelings using two open ended questions to facilitate the process, such as ‘How do you feel today?’ and ‘How was your training today?’ Parents will also be invited to enter comments in the diary, marked separately by their own cypher. All participants will be loaned a tablet device and shown how to record an e-diary using either text or voice input to record their thoughts about taking part in the study and undertaking exercise. The electronic tablet device will be password protected (known by the child, parents and researcher). Diary entry will be prompted by a text/email and the diary entry will be uploaded directly to an online diary created and managed by the CTU. Where Wi-Fi is unavailable, a device will be lent to the family with mobile data enabled. Motivational messages or badges will be sent via text or email to encourage the children to record their diary and to acknowledge receipt of an entry. The e-diaries will provide information about how the children experience their exercise programme and how this affects daily life over time.

### 14.6.2 Photo-elicitation interviews with the children

Photo-elicitation technique has been selected as it gives the children the opportunity to express their ideas in visual as well as verbal form and for the balance of control over data collection to be shifted to the child rather than the interview being driven by an adult agenda [19, 20]. The children will be able to either use the tablet or use their own camera/smartphone. The children will be asked to take photographs in week 9-10 of training, about the things they think are important about their allocated exercise regime (e.g., things they like and don’t like, things they think should be changed, things that make exercise hard or easy) as well as what they thought about the trial (e.g. length and content of measurement sessions, experiences of randomisation). When the child has taken the photographs and completed the training period the researcher will arrange to meet the child and discuss during the interview the photographs the child has taken. The children will select which of the photographs they wish to talk about and, as needed, prompt questions will be used to clarify the researcher’s understanding. An interview topic guide for the photographs will be developed and informed by the literature and the Patient Public involvement (PPI) Advisory Group. Those children using non-verbal communication aids will be interviewed with their facilitator and will be encouraged to record their feelings around their photographs and be given a set of questions to guide them before the interview to allow preparation of speech.

The interviews are likely to last between 20-45 minutes and will, as appropriate, be conducted without the guardian to allow the child freedom to express their own views. The use of arts based methods [21] will be used to allow children to illustrate what participating in the study meant to them including the outcome measurement process and the intervention itself.

Interviews will be planned after the 10-week data collection point by the researcher with n = 12 children. This avoids recall bias that would occur with interviews at the end of the overall study period (17 months). Although this leads to un-blinding, it is felt to be more important to obtain subjective views of the feasibility of the trial and factors affecting adherence soon after completion of the main phase of the study to better inform a later RCT.

### 14.6.3 Interviews with study parents and parents who withdraw or decline to participate

Study parents (n = 12-24): The child’s parents will be interviewed on the same day of the child’s interview, wherever possible. Depending on the parents’ consent and availability, the interviews will be conducted with either one parent or both parents if they wish/as appropriate. Semi-structured interviews using a topic guide will be used to facilitate data generation. The interviews will explore parents’ experiences of participating in the trial and the effect on family life of undertaking the intervention / home exercise programme.

Decliner and withdrawer parents (n = up to 8): Semi-structured interviews using a topic guide will be conducted with up to eight parents who declined or withdrew from the study prior to completion. Potential participants will be sensitively approached to see if they would consent to a five-minute phone call from the research team to see how we can participation more accessible and attractive and to help to identify and remove barriers to participation.

### 14.6.4 Individual interviews with physiotherapists

Four physiotherapists involved in the trial will be individually interview following the intervention period. This will provoke recollection of different experiences and opinions of the overall experience of the trial. It will help to evaluate whether the main RCT will be achievable, identify potential problems, and help to refine and improve them to inform the subsequent main RCT. The interview will be organised at the end of the trial data collection period and carried out either in person, or by telephone or video call.

### 14.6.5 Interview/focus group settings

All interviews will be conducted in the participants’ chosen environment. This is likely to be the child’s home and the clinician’s work setting. The interviews will be arranged on a date and time convenient to the participants.

### 14.6.6 Data management of Interview Data

Each study tablet will be password protected to ensure that data are secure when in the child’s home. The study tablets will be data wiped before being given to the next child. Interviews will be audio recorded, transcribed verbatim and anonymised. Photographs and the written dairy entries will be stored on encrypted hard drives.

## 14.7 Data Analysis

Anonymised transcripts of interviews, photographs, diary entries and field notes taken during the fieldwork will be imported into a qualitative data analysis computer software package, NVivo, to enable the organisation and analysis of the data. Photographs will be anonymised as needed. The qualitative data will be analysed in three separate groups:

 1) Child data (diaries and photo-elicitation interviews)

 2) Parent data (including those who withdrew or declined)

3) Physiotherapist data.

The textual data will be interrogated using Thematic Analysis methods [22].

The first analysis step will involve familiarisation of the text, and then the researcher will code the text by allocating the text fragments to codes. These codes may be revised during the process of reading the transcripts and subthemes developed. For the purpose of rigour, a small sample of data will be analysed by a second person. After this, the codes will be reviewed and themes will be formulated. Finally, meaningful text fragments, sub-themes and themes will be determined related to the study objectives.

Analysis of the photographs will follow the same thematic analysis strategy as described above where the researcher is coding for factors such as type of photograph, setting, people.

Themes arising from the diaries, interviews and photographs will be triangulated in order to check the consistency of the analysis and to generate a deeper understanding of the experience of the participants in order to draft recommendations for the main RCT.

### 14.7.1 Rigour and Credibility

Preliminary themes arising from the individual data will be feedback to the participants so they can judge whether the analytic interpretations reflect their experiences. This will take place within 2 weeks of the interview.

Checking of the quality of data will take place after every third interview data has been analysed. This quality assessment will be done by sharing the initial codes and themes with the PPI Advisory Group to seek their opinions/perspectives as well as during supervision sessions. Any data shared for this purpose will be anonymous. This will facilitate refinement of future analysis and topic guides.

The position of the researcher as an experienced paediatric physiotherapist could potentially be a limitation and introduce bias to both interviewing and the thematic analysis. For this reason, supervisors will act as a “reflecting team”.

Bias could be introduced, as the research fellow will be aware of which group the child and parents will have been allocated to at week 10. Although this is clearly a limitation, it was felt that as this is a feasibility study and the study is being run by one person (a doctoral student) that this limitation was acceptable as the priority should be to gain data to inform a successful full RCT.

# 15 END OF TRIAL

The end of trial is the point when all data queries for the trial have been satisfactorily concluded’. The following criteria will be considered during any assessment of the need to prematurely stop the studies:

* A decision made by the TSC on the grounds of safety issues, such as an unacceptable number of adverse events.
* An evaluation via a fully powered randomised controlled trial of a similar programme in people with CP.

# 16 SAFETY AND MANAGEMENT OF RISK

## 16.1 Participant safety

Physiotherapists will be setting up the interactive trainer for each child. The child with then use the trainer in a clinic, school or home. The treating physiotherapists require training with the device before using it in clinical practice. The PI will deliver training to the local teams as part of the trial set up and site visit. The CI will provide Standard Operating Procedures (SOP) in the form of a video to inform the treating therapist and carers. This will ensure that the device is set up correctly and that the adult responsible for supervising the child’s training receives training and information about the equipment in a consistently safe way. This SOP will include a manual handling assessment of moving the device and helping the child into and out of the trainer. The PI will agree a contract with the family or carer before training to ensure that the device is used in the intended way and is kept in good working order within the terms of the Trial’s insurance. The SOP will also detail how to arrange repairs in the event of a problem.

## 16.2 Therapist Safety

All Treating and Research Therapists will comply with the standard health and safety procedures of their employing organisation. Research therapists will adopt the University of Plymouth lone working policy when undertaking any visits within the participants’ home.

This trial is categorised as Type A = No higher than the risk of standard medical care

# 17 ADVERSE EVENTS

## 17.1 Recording and reporting of AEs

An adverse event (AE) is defined as any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease that develops or worsens during the period of the trial, whether or not it is considered to be related to the trial intervention. The risks of taking part in this trial have been assessed to be low. AEs such as chest infections, urinary tract infections, diarrhoea / constipation, and spasms, which are common in children with CP, will NOT be reported for any participants. Any new or worsening problems, which participants and or therapists perceive to be related to participation in the trial, will be captured.

Examples of AEs that require reporting include:

* Aches and pains in the leg muscles following training, lasting over 1 hour or requiring pain relief
* Injury related to the training
* Fatigue lasting more than 1 day following training

AE will be recorded in a sheet attached to the intervention diary. Participants will be asked to complete this sheet from the point of randomisation until the final assessment. The AE sheet and diaries will be returned by stamped addressed envelope or e-mail every month. Recorded AEs and SAEs will be presented to the monthly TMG meeting for review. The TMG will refer concerns to the TSC for further review if required.

Participant’s parent/guardian will be asked to report any AE’s that occur following the baseline assessments to the PI/CI.

AEs considered related to either intervention or control groups will be followed until resolution or the event is considered stable. It will be the responsibility of the clinical care team, in discussion with the CI, whether or not an AE is of sufficient severity to withdraw the participant from the intervention. The participant may also voluntarily stop participating in the intervention arm due to what he or she perceives as an intolerable AE.

## 17.2 Recording and reporting of SAEs

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

1. results in death;
2. is life-threatening;
3. 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;
4. results in persistent or significant disability or incapacity;
5. consists of a congenital anomaly or birth defect; or
6. Is otherwise considered medically significant by the investigator.

SAEs will be recorded from baseline assessment until the date the participant completes follow-up or withdraws from the study.

SAEs may be volunteered by the participant or discovered by the Treating Therapist or Research Therapist 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 and treating therapists will be asked to report any SAEs directly to the trial co-ordinator 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 the trial. Any SAE will be reported within 24 hours of the research team becoming aware of it. Serious adverse events will be recorded from the time of the baseline

It is not anticipated that there will be any SAEs related to the trial, but any Unexpected Serious Related Event will be reported to REC within 15 days of CI being informed.

## 17.3 Responsibilities

 Principal Investigator (PI):

Checking for AEs when participants attend for treatment / follow-up.

1. 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.
2. 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 the allocated group. 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.
3. If the PI considers that the SAE is not, or is unlikely to be, related to the trial, then this will be discussed with the CI (or if unavailable another appointed member of the research team) to obtain a second assessment of causality.
4. Ensuring that AEs are recorded and reported to the CI

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

1. Clinical oversight of the safety of patients participating in the trial, including an ongoing review of the risk / benefit.
2. Ensuring that SAEs are sent to the sponsor within 2 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.
3. Review of specific SAEs in accordance with the trial risk assessment and protocol as detailed in the Trial Monitoring Plan.
4. Reporting safety information to the Trial Steering Committee (TSC)
5. Central data collection and verification of AEs, SAEs, according to the trial protocol onto study database.

Trial Steering Committee (TSC):

In accordance with the TSC charter, periodically reviewing safety data.

# 18 STATISTICS AND DATA ANALYSIS

## 18.1 Sample size calculation

As this study is a feasibility trial, it is not appropriate to use a sample size calculation based on considerations of power for detecting between group differences [23]. The feasibility aims are to provide robust estimates of recruitment rate and follow up as well as estimates of the variability of the outcome measures, which will in turn inform sample size calculations for a full RCT.

A sample size of 40 participants sample size will allow the overall recruitment rate to be estimated it is anticipated that follow-up a minimum of 12 participants in each of the two treatment groups would provide sufficient data to inform indicative sample size calculations for the definitive main trial. However recruiting 40 participants will allow a estimation of retention rates with a level of precision of at least =/- 16% (95%CI) [24].

### 18.1.1 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 CDC area there will be approximately 150 children with a diagnosis of CP (Cerebral Palsy Integrated Pathway South West, 2017 unpublished data) [14]. Therefore, we predict that approximately 60-80 ambulant children with CP may be eligible in each CDC area.

We aim to recruit 40 participants across five sites in Devon and Cornwall over 12 months. Two interactive exercise devices are owned by Torbay and South Devon NHS Foundation Trust (TSDFT) and will remain in this area whilst the other two devices can be allocated outside of this area. Recruitment of 20 participants will be from TSDFT over the course of the study. The remaining sites will recruit four children each. Recruitment will be staggered by area to allow the transportation of the two interactive exercise devices in a logical and efficient way.

An estimated recruitment rate of three to four children per month over a 12-month period has been calculated based on population and previous experience.

## 18.2 Analysis populations

All analyses and data summaries will be conducted on the intention-to-treat (ITT) population which is defined as all participants randomised regardless of non-compliance with the protocol or withdrawal from the study. Participants will be analysed according to the intervention they received.

## 18.3 Interim analysis and criteria for the premature termination of the trial

There is no interim analysis planned. The TSC will receive a quarterly report of all AEs and SAEs. If safety concerns arise, the chair of the TSC will contact the trial coordinator to review this.

## 18.4 Quantitative Analysis Plan

Prior to database lock, a detailed statistical analysis plan (SAP) will be developed by the CI with advice from the trial statistician. The plan will conform to guidance related to statistical analysis plans [25], and take into consideration CONSORT guidance for reporting feasibility and pilot trials [26], CONSORT Patient-Reported Outcome (PRO) [27] and CONSORT statement for randomised trials of non-pharmacological treatments [28].

For the final analysis, the data will be presented in an anonymised form, maintaining concealment of group allocation. Only after primary analysis, will group allocation be revealed. Analysis will be done by the CI with guidance from the Trial statistician.

### 18.4.1 Participant Population

Participant progression through the trial will be reported via a CONSORT diagram and will be described using baseline characteristics including:

* Age
* GMFCS level
* Impairment
* Gender

### 18.4.2 Feasibility Analysis

The feasibility outcomes will be summarised using descriptive statistics. Data from screening, recruitment rate and source, withdrawals will be used to generate realistic estimates for the full trial. Completion rates of the intervention and outcomes collected at each time point will be reported with confidence intervals. The baseline characteristics of those lost to follow up will be compared to those who complete the trial in order to identify any potential bias.

### 18.4.3 Potential primary and secondary outcome analysis

The planned primary and secondary outcome measures will be reported at each time point using descriptive statistics. As this is a feasibility trial, it is not appropriate to perform a hypothesis test between-group treatment effects [23]. Instead, the difference between allocated groups of the follow-up minus baseline score will be estimated with confidence intervals.

### 18.4.4 Definitive Trial Sample Size Estimation

A sample size estimate for a definitive trial will be undertaken for the proposed primary outcome. Estimation of the standard deviation, correlation between baseline and follow-up measures and a clinically meaningful difference will be used in the power calculation.

## 18.6 Missing Data

Missing outcome data will be summarised at each time point. In particular:

* **Next Step test** – data will be checked for artefact and missing markers. The motion analysis system is able to interpolate for missing markers. In the presence of >10% missing marker data the data for that trial will be discarded. Marker availability is assessed on a trial-by-trial basis and adjustments can be made during the study session if markers become out of view due to a reduction in battery life or occlusion of markers (e.g. by clothing).
* **Participant recorded diary** – number of days of diary data will be reported, including a percentage of the total number of days.

## 18.7 Triangulation of data and progression criteria

Results from all aspects of the qualitative data will be triangulated with the results of the qualitative aspects of the study. The triangulated data will determine the suitability of the protocol for incorporation into the main RCT.

Progression criteria, determined in advance of recruitment and in consultation with the TMG will include minimum recruitment and retention rates (~70%) and a 90% completion rate of our outcome measures. Failure to achieve these will indicate that a full trial is not feasible unless our qualitative study indicates clear means by which the rates may be improved. A recommendation list will be generated to enable refinement of the subsequent RCT protocol.

# 19 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 study site visits as appropriate and will be reviewed and agreed by the TMG. 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 allocation to trial groups, adherence to trial interventions 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 Good Clinical Practice.

# 20 ETHICAL AND REGULATORY CONSIDERATIONS

## 20.1 Research Ethics Committee (REC) review & reports

The trial 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.

The Trial Steering Committee and the Sponsor reviewed this trial protocol. 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 Trial 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.

## 20.2 Peer review

An independent team of clinical academics as part of the NIHR clinical doctoral fellowship application has reviewed the study. In addition, the trial has been peer reviewed by the lead researcher at PENCRU – Peninsula Cerebra Research Unit and Lead therapist and Researcher at Dame Hannah Rogers Trust.

## 20.3 Public and Patient Involvement

* Design of the research- Families have been consulted on the design of the trial especially the two assessment visits. 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.
* A group of PPI representatives (PPI Advisory group) will be invited to take part in qualitative analysis by checking emerging themes.
* Dissemination of findings- The family faculty at PENCRU will advise on appropriate dissemination of the results in order to reach families in the most accessible way.
* Payment for PPI will be in line with the INVOLVE guidance.

## 20.4 Regulatory Compliance

Before any site can enrol patients into the trial, 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/ Principal Investigator 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).

## 20.5 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.

## 20.6 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 trial conduct phase:

a) The safety or physical or mental integrity of the subjects of the trial

b) The scientific value of the trial

c) The conditions and principles of GCP in connection with that trial

The sponsor will be notified within 7 days of becoming aware of any accidental breach / amendment to the trial protocol. The sponsor will be required to adjudge amendments prior to submitting these to REC/HRA.

## 20.7 Data protection and patient confidentiality

All investigators and trial 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 the linking code will be stored on the secure study database. This will be stored for the duration of the trial 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-investigators
* Rachel Rapson is the data custodian for the duration of the trial. Once the trial is completed, the CI (Rapson) is responsible for the long-term storage of data in accordance with University of Plymouth regulations.

## 20.8 Financial and other competing interests

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

## 20.9 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
* Arising from harm to participants in the conduct of the research

## 20.10 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 Trial Master File and Investigator Site Files.

## 20.11 Post trial care

Where treatment is required beyond the length of the trial, the CI will liaise with the local therapist to ensure that the patient is able to access care.

# 21 DISSEMINIATION POLICY

## 21.1 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 Trial Report prepared
* Study findings will be published in peer reviewed academic journals and presented at National and International conferences.
* NIHR 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.

## 21.2 Authorship eligibility guidelines and any intended use of professional writers

The CI and trial management group will have authorship on the final trial report

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# 23 APPENDICIES

## 23.1 Appendix 1 – Authorisation of participating sites

These will be attached following ethical / R and D approval

### 23.1.1 Required documentation

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

### 23.1.2 Procedure for initiating/opening a new site

New sites will be included after application by the CI to the HRA.

### 23.1.3 Principal Investigator responsibilities

Local PIs who will be responsible for participant identification at NHS sites will be expected to attend a training session about the trial. This will include training about the study aims and design and on data management and protection requirements.

The PI’s responsibilities include arranging the initial site visit, coordinating and storing the interactive trainer. The PI will ensure that the local therapist will treat the participants in accordance to the protocol and report AE and SAE’s.

## 23.2 Appendix 2 – Schedule of Procedures

|  |  |
| --- | --- |
| **Procedures** | **Visits (insert visit numbers as appropriate)** |
| **Screening** | **Baseline** | **Treatment Phase** | **Follow Up** |
|  |  | Week 0 | Week1 | Week 5 | Week 10 | Week 20 |
| Informed consent |  | x |  |  |  |  |
| Demographics | x | x |  |  |  |  |
| Medical history | x | x |  |  |  |  |
| Physical examination |  | x |  |  | x | x |
| Randomisation |  | x |  |  |  |  |
| Assessment 1 Next Step testWalking kinematicsMuscle power of quadriceps, hamstrings, gastrocnemius and hip abductors Passive range of movement and Tardieu scale of quadriceps, hamstrings, gastrocnemius and hip COPMCHU-9D |  | x |  |  | x | x |
| Assessment 2 Participant recorded diary |  | x | x | x | x |  |
| Assessment 3 Qualitative interview |  |  |  |  | x |  |
| Adverse event assessments  |  |  | x | x | x | x |

## 23.3 Appendix 3 – Safety Reporting Flow Chart



## 23.4 Appendix 4 – Amendment History

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Amendment No.** | **Protocol version no.** | **Date issued** | **Author(s) of changes** | **Details of changes made** |
| 1 | V2 | 11.09.2020 | RRapson | TMG has agreed that we should not train sites on usual care but record how each sites usual care varies from the guidelines on usual care. Therefore the amendment removes wording which refers to training each site in usual care. Progressive strengthening has been removed as a literature search revealed poor evidence to support its use as part of usual care. Secondly the protocol states the CHU-9D as the questionaire but it is incorrectly stated as CPQOL in the parent-guardian and young person PIS and the CPQOL was uploaded to IRAS instead of the CHU-9D.  |