BMJ Open

BIKE SKILLS TRAINING FOR CHILDREN WITH CEREBRAL PALSY: PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019898
Article Type:	Protocol
Date Submitted by the Author:	03-Oct-2017
Complete List of Authors:	Toovey, Rachel; Murdoch Childrens Research Institute, Developmental Disability and Rehabilitation Research; University of Melbourne, Physiotherapy Harvey, Adrienne; Murdoch Childrens Research Institute, Developmental Disability and Rehabilitation Research; The Royal Children's Hospital, Melbourne, Neurodevelopment and disability McGinley, Jennifer; University of Melbourne, Physiotherapy Lee, Katherine; Murdoch Children's Research Institute, Melbourne Children's Trials Centre; University of Melbourne Shih, Sophy; Deakin University, Deakin Population Health Spittle, Alicia; University of Melbourne, Physiotherapy; Murdoch Childrens Research Institute, Victorian Infant Brain Studies
Keywords:	Cerebral palsy, Physical activity, Participation, Children

BIKE SKILLS TRAINING FOR CHILDREN WITH CEREBRAL PALSY: PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL

Investigator names:

Rachel Toovey[1, 2, 3] Adrienne R. Harvey[2, 4, 5], Jennifer L. McGinley[1], Katherine J. Lee [5, 6, 7], Sophy T.F. Shih[8], Alicia J. Spittle[1, 9]

Institutional affiliations:

1. Department of Physiotherapy, University of Melbourne, Melbourne, Australia
2. Developmental Disability and Rehabilitation Research, Murdoch Children's Research Institute, Melbourne, Australia
3. Victorian Paediatric Rehabilitation Service, Monash Children's Hospital, Melbourne, Australia
4. Neurodevelopment and Disability, The Royal Children's Hospital, Melbourne, Australia
5. Department of Paediatrics, University of Melbourne, Melbourne, Australia
6. Clinical Epidemiology and Biostatistics Unit, Murdoch Children's Research Institute, Melbourne, Australia
7. Melbourne Children's Trials Centre, Melbourne Children's Campus, Melbourne, Australia
8. Deakin Health Economics, Centre for Population Health Research, Deakin University, Geelong, Australia
9. Victorian Infant Brain Studies, Murdoch Children's Research Institute

Corresponding author: A/Prof Alicia J. Spittle. Department of Physiotherapy, University of Melbourne, Alan Gilbert Building, 161 Barry St, Carlton 3053. Email: aspittle@unimelb.edu.au

Funding: This work was supported by a Physiotherapy Research Foundation Seeding Grant (S16-007), an Australian Government Research Training Program Scholarship (RT), National Health Medical Research Council (NHMRC) Centre of Research Excellence in Cerebral Palsy ID 1057997 (RT, ARH. SS), Centre of Research Excellence in Newborn Medicine ID 1060733 (AJS), NHMRC Career Development Fellowship ID 1053767 (AJS), Melbourne Children's Campus Clinician Scientist Fellowship (ARH), Murdoch Children's Research Institute (RT, ARH and KJL) and the Victorian Government's Operational Infrastructure Support Program.

Completing interests: The investigators have no conflicts of interest to declare. The main funding body of this trial (Physiotherapy Research Foundation) has had no role in the study design or procedures and will have no role in reporting and associated publications.

ABSTRACT

Introduction: Two-wheel bike riding can be a goal for children with cerebral palsy (CP) and a means of participating in physical activity. It is possible for some children with CP to ride a two-wheel bike, however, currently far fewer can ride compared with their typically developing peers. Evidence supports training targeted towards goals of the child with CP and their family; yet there is little evidence to guide best-practice bike skills training. Task-specific training may lead to attainment of two-wheel bike specific goals. This study aims to determine if a novel task-specific approach to training two-wheel bike skills is more effective than a parent-led home program for attaining individualised two-wheel bike specific goals in independently ambulant children with CP aged 6-15 years.

Methods and Analysis: Sixty eligible children with CP (Gross Motor Function Classification System levels I-II) aged 6 – 15 with goals relating to riding a two-wheel bike will be randomised to either a novel task-specific centre-based group program (intervention) or a parent-led home-based program (comparison), both involving a one week intervention period. The primary outcome is goal attainment in the week following the intervention period (T1). Secondary outcomes include; goal attainment and participation in physical activity at three months post intervention (T2) and bike skills, attendance and involvement in bike riding, self-perception and functional skills at T1 and T2. Economic appraisal will involve cost-effectiveness and cost-utility analyses. Adherence of clinicians and parents to the intervention and comparison protocols will be assessed. Linear and logistic regression will be used to assess the effect of the intervention, adjusted for site as used in the randomisation process.

Ethics and dissemination: This study was approved by the Human Research and Ethics Committees at the Royal Children's Hospital (#36209). Results will be disseminated via peer-reviewed publications and conference presentations.

Registration: NCT03003026; pre-results, recruitment ongoing.

STRENGTHS AND LIMITATIONS

- To our knowledge, this will be the first powered randomised controlled trial to evaluate the effectiveness of a novel task-specific bike skills training program for attaining bike-specific goals in children with cerebral palsy
- The range of secondary outcomes will allow for assessment of the effect of training bike skills on a range of activity and participation outcomes
- Assessment of fidelity will enable evaluation of the extent to which clinicians and families adhere to the intervention and comparison group protocols
- The economic appraisal will be useful for future policy and decision-making
- Due to the nature of the intervention, clinicians delivering the interventions and participants will not be blind to allocation

Key words

Cerebral palsy

Physical activity

Participation

Children

INTRODUCTION

Cerebral Palsy (CP) is the most common cause of childhood physical disability affecting one in five hundred births[1]. It is a group of disorders of the development of movement and posture, causing activity limitations that are attributed to non-progressive disturbances occurring in the developing foetal or infant brain[2]. Children with CP participate less in physical and recreational activities than their typically developing peers[3], putting them at increased risk of poor health and disease in adulthood[4]. Effective means of engaging children with CP are required to improve physical activity patterns in this population, and evidence supports training targeted towards goals of the child and their family[5]. Bike riding is a common activity for families[6] and may be an effective means of involving ambulant children with CP in physical activity that is enjoyable and meaningful to them.

The Gross Motor Function Classification System (GMFCS)[7] uses five levels (I-V) to classify children with CP according to their level of motor function. Children classified as levels I-II are independently ambulant with or without hand-held devices. Far fewer ambulant children with CP (GMFCS I-II) can ride a two-wheel bike at any given age compared to their typically developing peers, and if they do, they learn later in life. However, it is possible for children with CP at GMFCS levels I and II to learn to ride and the majority who do so, learn at home with their parents[8].

Despite physiotherapists and occupational therapists implementing training to improve motor skills in children with CP, there is very little specific evidence to guide best practice in training of bike riding skills. The studies that do exist specific to children with CP have been conducted on stationary bikes[9-11] with no evidence to suggest this translates to riding a two-wheel bike in the community. Further, the current practices of Australian physiotherapists and occupational therapists for training two-wheel bike skills in children with CP are not well understood. Importantly, there does not appear to be a standard or usual care.

The development and testing of approaches to training bike skills is required to provide clinicians and families with evidence-based guidance when working with children with CP with two-wheel bike specific goals. Strong evidence exists for task-specific training to improve general upper limb function in this population[5 12] and gross motor skills in adults following stroke[13]. Task-specific training involves practice of context-specific tasks where the intervention focuses on the skills needed for a task(s)[14]. It is informed by principles of motor learning[15] and dynamic systems theory[16] and involves a dynamic interaction between the task, the child and the environment to achieve a motor skill in a task-specific context[17]. Evidence for task-specific training to improve gross motor skills in ambulant children with CP exists[18 19], but is currently limited by poor study methodology and intervention heterogeneity. An intensive task-specific approach to training bike skills has seen promising outcomes in a group setting at the two main paediatric rehabilitation settings in Victoria, Australia demonstrated through results from a small pilot case series (n=5)[20]. Whilst this clinical evidence supports the safety and feasibility of task-specific training in bike riding in a group setting, an adequately powered study with a comparison group is required to ascertain the effectiveness of such an approach.

Objectives

The primary objective of this study is to determine if a novel task-specific approach to training bike skills is more effective than a parent-led home program in ambulant children with CP (GMFCS I-II) aged 6 - 15 years, for attaining individualised two-wheel bike specific goals immediately following the intervention period (T1).

The secondary objectives of this study are:

1. To determine if a novel task-specific approach to training bike skills is more effective compared to a parent-led home program in children with CP (GMFCS I-II) aged 6 - 15 on
   a. Goal attainment at three months following the intervention (T2)
   b. Acquiring and retaining two-wheel bike skills at T1 and T2
   c. Functional skills at T1 and T2.
   d. Physical activity behaviour at T2
   e. Self-perception at T1 and T2
   f. Self-perceived bike riding competence at T1 and T2
2. To compare attendance and involvement in bike skills training between the intervention and comparison groups during the intervention and follow up periods
3. To conduct an economic appraisal, involving assessment of quality of life, of the intervention compared to the comparison program
4. To examine clinician and parent fidelity with delivery of both group protocols

METHODS AND ANALYSIS

Design

Assessor-blinded, parallel group, randomised controlled, multicentre, superiority trial comparing a novel task-specific approach to a parent-led home program for training bike skills. This study involves a one week intervention period and three month follow up period (Figure 1).

Setting

The study will be conducted through the Victorian Paediatric Rehabilitation Service (VPRS: a state wide rehabilitation service for children with rehabilitation goals including children with CP) at the Royal Children's Hospital and the Monash Children's Hospital in Melbourne, Australia.

Participants

Sixty participants will be recruited from the Victorian Cerebral Palsy Register (VCPR: a register of children with CP who were born in Victoria or receive health services in Victoria) and the VPRS. Approximately 30 children will be randomised to the intervention group and 30 children will be randomised to the comparison group

(Figure 1). Each participant must meet all of the inclusion criteria and none of the exclusion criteria to be enrolled in this study (Table 1).

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Is between 6 - 15 years old at the time of randomisation • Has CP as determined by the VCPR or in writing from the child's general practitioner or paediatrician if not on the VPCR • Is independently ambulant without aids (GMFCS I-II) • Has goals related to improving two-wheel bike skills • Has a primary caregiver available to participate in the intervention • Has a legally acceptable representative capable of understanding the informed consent document and providing consent on the participant's behalf • Lives in Victoria or close to the Victorian border in New South Wales and receives health services in Victoria • Has access to an appropriately sized two-wheel bike and helmet • Has medical clearance to participate in the study from the child's general practitioner, paediatrician or paediatric specialist • Participant and primary caregiver able to understand English	• Has a moderate to severe intellectual impairment • Has a dual diagnosis with another developmental disability or medical condition that may impact on their ability or safety to train two-wheel bike skills • Had musculoskeletal surgery, or other major surgery including insertion of a baclofen pump that may affect their physical ability in the 6 months prior to randomisation • Had Botulinum toxin-A injections to the lower limbs and/or upper limbs in the six months prior to randomisation

Recruitment procedures

Participants will be identified and recruited through the VCPR and the VPRS at the Royal Children's Hospital and Monash Children's Hospital. The study will also be advertised on the National Health and Medical Research Council (NHMRC) Centre of Research Excellence in Cerebral Palsy (CRE-CP) newsletter and website.

Victorian Cerebral Palsy Register

Within this register, it is recorded whether parents or primary care givers have consented to being contacted for research purposes. Invitations to participate in the study will be sent by VCPR staff to potentially eligible participants whose parents/primary care givers have provided consent by email or letter including a full participant information and consent form. Families will have the opportunity to contact the VCPR to request that their contact details not be passed onto the study team for follow up and screening for eligibility which will occur by email and phone.

The Victorian Paediatric Rehabilitation Service

Waitlists for services and clinics at VPRS sites at The Royal Children's Hospital and Monash Children's Hospital, will also be used to identify potentially eligible participants. A VPRS clinician will contact the parents of potentially eligible participants as per respective VPRS site physiotherapy waitlists. Potentially eligible participants who attend VPRS clinics at both hospitals during the recruitment period but are not yet on the respective VPRS physiotherapy waitlists will also be identified by VPRS clinicians. Interested families will be given the study contact's details or permission will be sought by the VPRS clinicians to pass their contact information on to the study contact for screening and follow up.

The Centre for Research Excellence in Cerebral Palsy website and e-newsletter

An advertisement inviting eligible families to participate in the study will be posted on a parent, clinician and researcher website for the management and treatment of CP (http://www.cre-cp.org.au) and in the website's e-newsletter during the recruitment period.

Baseline study visit

Eligible participants will be enrolled in the study at the baseline (T0) assessment visit up to 6 weeks prior to the intervention period. Written informed consent will be obtained prior to performing any assessments and randomisation by Principal Investigator or trained outcomes assessor. The following will be collected at the T0 assessment (see also Appendix 1):

- Age, intellectual impairment (if any) and details of the CP including: topography, motor type, GMFCS level and Manual Ability Classification System level
- Previous time spent practicing bike skills on average per week or month since commencement of bike skills practice
- Parent rated importance of their child attaining their goals, competence of their own bike skills and family interest in bike riding on a five point adjectival scale
- Family social risk as measured by a questionnaire comprised of six questions regarding social status including family structure, education of primary

caregiver, occupation of primary income earner, employment status of primary income earner, language spoken at home and maternal age at birth[21]

- Goals will be set by the child, parent and outcomes assessor together using the Goal Attainment Scale (GAS)[22]
- Baseline data for secondary outcomes including: two wheel bike skills, functional skills, physical activity behaviour, self-perception, self-perceived two-wheel bike riding competence and health-related quality of life as assessed by the measures detailed below under "Primary and secondary outcome measures."

Randomisation and blinding

A statistician not directly involved in the study will prepare the randomisation schedule using computer-generated block randomisation with variable block sizes. Randomisation will be stratified by site. The statistician will generate opaque, numbered, sealed envelopes according to the randomisation schedule. In the week prior to the intervention period the participant will be allocated a sequential study number within the appropriate strata. Participants will then be randomised by a study investigator not involved in assessment procedures who will open the envelopes inform participants of their allocation via phone or email. Participants are already known to either site will be randomised within that site, otherwise families will be randomised within a site based on family preference or home location. The outcome assessors will be blind to group allocation but it will not be possible to blind the treating clinicians or participants.

Details of the intervention and comparison

The intervention: Novel task-specific bike skills training program

Participants randomised to the intervention group will participate in a novel bike skills training program conducted over three consecutive days, with a further four days for practicing the learnt skills at home (seven-day intervention period). The intervention involves seven key components:

1. Task-specific: Training will be informed by the dynamic systems theory and principles of motor learning. The dynamic interaction between systems including the task, the child and the environment is considered to achieve motor skills in a task-specific context [16]. Each of these systems is considered at each stage of the motor learning process. Initially new motor tasks are scaffolded, so that the participant will always actively complete at least part of the task. This may involve task demonstration or physical guidance. As performance improves, the task and/or environment in altered to encourage problem solving and increase the motor challenge. This may include modifying the bike (e.g. seat height, location of the brakes, basic straps for hand or feet) and reducing the physical guidance in order to achieve each progression of the skill/s. Once a motor skill is acquired, variability and randomness of practice in terms of task difficulty and environmental challenge will be introduced to increase the complexity and generalisability of the skill[23]. Overall practice will be repetitive,

progressive, variable and favour whole skill practice rather than part practice[23]. The amount and type of feedback from the trainer will be guided by participant preference, and will focus on knowledge of results or performance for each new skill [24], for example getting on and off the bike. Participants will utilise their own two-wheel bike without training wheels and helmet where possible. Cones or markers will be used as a visual cue for skill practice.

2. Group-based: Training will be delivered to groups of up to six participants. There is evidence to suggest group-based rehabilitation programs improve functional skills, self-perceived performance and cost-effectiveness of treatment as much, or more than individual therapy [25].
3. Clinician-mediated: Each program will be conducted by at least one physiotherapist and one other clinician (physiotherapist, occupational therapist or allied health assistant). There will be a minimum ratio of one clinician to three children participants in each group. All clinicians will be employed by VPRS and will undertake six-eight hours training in the intervention protocol in the four months prior to delivering the intervention. The same two clinicians will lead the three days of each program.
4. Intensive: Each program will run for two hours per day over three consecutive days during one week of the school holiday period. This intensity is supported by motor learning literature, in particular the benefits of repetitive practice in the skill acquisition phase[26]. This intensity allows for repetitive practice[18], including repetitive practice in the home environment following the program and has been supported by parent evaluation of the intensive program delivered as part of the pilot case series[20]. Breaks from physical activity will be offered at least every 30 minutes and families can request additional rests. Participants will also be given a home program of one to three bike skills practice exercises following each session and encouraged to practice these up to 30 minutes per day during the week-long intervention period and three to five bike skills to practice when able in the three month follow up period.
5. Goal-directed: Evidence suggests interventions that are goal-directed improve gross motor function more than those that are not[27]. Goal setting is a key component of paediatric rehabilitation and has been well established in the literature [28]. The Goal Attainment Scale (GAS) will be used as an outcome measure and as a process for setting goals related to bike skills training. Clinicians delivering the intervention will be aware of each participant's goals, which will be used to provide individualised opportunities for problem solving and drive the movements required to meet the task demands[29 30].
6. Parent or caregiver involvement: At least one parent or caregiver will be required to attend each session of the program. Parent involvement and education is recognised as a key component in family-centred practice[31]. It facilitates a partnership between the clinician and parent towards achieving the child's goal. Parents will be coached by the clinician during the three-day intervention regarding approaches to motor learning, including gradually increasing the difficulty of the task whilst ensuring this intersects with success. Parents will be provided verbal guidance regarding strategies and safety of practice in the home environment[23].
7. Ecological setting: When possible the program will be conducted in outdoor recreation or community reserves at or in close proximity to the rehabilitation

service. This aligns with dynamic systems theory and task-specific training in terms of the role the environment has in promoting motor learning. Different surfaces and gradients will be available to individualise the environment based on each participant's stage of motor learning and to promote successful problem solving. All program settings will be conducted away from road and busy public spaces. Participants will be encouraged to practice outside of the program in similar environments and advised to avoid practice on roads, busy bike paths or other risky environments during the intervention or follow up periods.

The comparison: Parent-led home bike skills training program

Current bike skills training for children with CP is not well understood. Given the lack of specific evidence, current practice is not likely to be uniform in approach, dosage or setting. Whilst the majority of ambulant children with CP (GMFCS I-II) are currently not able to ride a two-wheel bike, many of those who can ride learnt in informal settings with their families[8]. There also is evidence to support home-based therapy programs involving parent education for goal attainment in children with CP [5] [32]. Given this, it seemed appropriate that the comparison group for the intervention was a parent-led, home-based program.

Participants randomised to the comparison group will receive written general information on training bike skills either in person or via email dependent on consenting and baseline assessment location. Families will receive this information at the start of the one-week period of training during the school holidays. Parents will be encouraged to work with their child on two-wheel bike skills goals guided by the written information (available on request). This information involves:

1. Intensity: Families will be encouraged to practice at least 30 - 45 minutes on each of the seven days of the one-week period.
2. Safety: Families will be encouraged to practice in settings away from roads and busy public spaces. They will also be advised to perform a risk assessment of the location prior to commencing. Information on appropriate weather and adequate hydration will also be included.
3. Appropriate bike and helmet fit: Information regarding fitting the bike and helmet to the child for skill development, safety and potentially useful modifications

A trained VPRS physiotherapist will also telephone families in the comparison group between three-five days into training period. This phone call will involve asking the parents how the home program is going and providing general advice regarding practice for the remaining two-four days of the training period.

Primary and secondary outcome measures

Outcomes will be measured in the week following (T1) and three months (12-14 weeks) following (T2) the intervention period (Appendix 1). Outcomes will be assessed by the Principal Investigator (RT) or a physiotherapist trained in the outcomes assessment.

The primary outcome, goal attainment at T1, will be measured using the GAS, a criterion referenced tool for individualized and collaborative goal setting between the child, family and clinician[22 28 33]. The GAS is commonly used in rehabilitation for children with CP because it is valid[33], reliable and responsive[34] in this heterogeneous population. The GAS will be facilitated by the blinded outcomes assessors, trained in administering the GAS. Two to three individualized and measurable two-wheel bike specific activity or participation goals per participant will be set at the baseline visit (T0). Six potential outcomes will be specified for each goal: -3 (deterioration), -2 (equal to start), -1 (less than expected), 0 (expected), 1 (somewhat more than expected), 2 (much more than expected).[35] Children aged 8 – 15 will lead the goal setting at T0 and scoring of goal attainment at T1, whilst children aged 6 – 7 will complete the process with their parent and clinician. The primary outcome, goal attainment, is defined as attainment of at least one goal to an expected (score of zero) or greater level. While varied interpretations of goal attainment have been used, including averaging the number of goals achieved, recent literature in rehabilitation suggests that the chosen definition reflects a clinically relevant change and allows for appropriate statistical analysis, in that it is not treated as a continuous variable[35 36 37] .

The secondary outcomes will be assessed as follows:

- Goal attainment at T2 measured using the GAS[28]
- Bike skills acquisition and retention measured using the subscale items related to bike skills in the mobility domain of the functional skills in the Dutch calibration of Paediatric Evaluation of Disability Inventory (PEDI-NL)[38] and the Cycling Skills Checklist[39] at T1 and T2. The PEDI is a commonly used scale to measure functional status across the domains of self-care, mobility and social function in children with disability. As part of its calibration for use in the Netherlands, a subscale was added to the mobility domain involving four levels of bike riding skill. The PEDI-NL has good content and discriminative validity and is reliable in children with disabilities[40]. The Cycling Skills Checklist is a 20 item checklist of beginner bike skills where a score out of five is given for each skill. The maximum score for the highest level of bike skills is 100. It has not been validated in children with CP however has been used in research with children with Down syndrome[41].
- Functional skills measured using the PEDI-CAT[42] (computer adaptive test) at T1 and T2. The PEDI-CAT is a comprised of a comprehensive item bank of 276 functional activities acquired throughout infancy, childhood and adolescence. The PEDI-CAT measures function in four domains: (1) Daily Activities; (2) Mobility; (3) Social/Cognitive, and (4) Responsibility. It is valid and reliable for use in parents of children with all ages with CP. The Content-Balanced version of the PEDI-CAT will be used.
- Physical activity behaviour measured using a triaxial accelerometer[43] and the Physical Activity Questionnaire for Children (PAQ-C)[44] at T2. Accelerometry is a feasible, reliable and validated method of measuring activity in children and young people with CP[45]. The Activ8 ™ has been chosen as it is able to distinguish cycling as a different type of physical activity from walking, running, standing and sitting[43]. The Activ8 ™ will be worn by each participant for 7 days at T0 and at T2. The Physical Activity Questionnaire for Children

(PAQ-C) is a valid and reliable[46] self-report 7-day recall assessment of physical activity in children aged 8-20 years.

- Overall self-perception measured with the Pictorial Scale of Perceived Competence and Social Acceptance for Young Children[47] (ages 6-7 years) or the Self Perception Profiles for Children[48] (ages 8-13 years) and Adolescents[49] (ages 14-15 years) at T1 and T2. These self-perception scales have good validity valid in children without intellectual impairment[47-49].
- Self-perceived bike riding competence measured with using the bike-riding item of the Pictorial Scale of Perceived Movement Skill Competence[50]. The scale from which this item is drawn has good reliability, and face and construct validity in children[50 51].
- Attendance and involvement for participants in the intervention group during the 3-day program as recorded by clinicians delivering the intervention group protocol. Any home-based bike skills training during the intervention period in both groups will be recorded by participants and parents each day of the intervention period and each week during the follow up period in a participant diary. Families will also be asked to assess the involvement of the child of a five point adjectival scale from minimally involved to very involved in the practice for each day of the seven-day intervention period.
- Quality of life measured by Child Health Utility-9D (CHU-9D)[52] at T1 and T2. The CHU-9D is a paediatric generic preference based measure of health related quality of life[52]. It consists of a descriptive system and a set of preference weights, giving utility values for each health state described by the descriptive system, allowing for calculation of quality-adjusted life-years for cost utility analysis. It consists of nine domains and has been validated in children aged 7-17 years. Data of resources and time used to deliver the task-specific approach to training bike skills and the parent-led home program will be collected by clinicians and parents and used for cost-effectiveness analysis.
- Fidelity assessed by examining the adherence of the clinicians and parents to the intervention and comparison group protocols. The amount of time practicing bike skills will be measured by participant diaries in both groups. Clinicians will also complete attendance logs for participants in the intensive program intervention group and will document adherence to the protocol as reported by the parent on the comparison group phone call. Specific fidelity to the intervention protocol will be by video analysis. One session of the intensive program per participant will be videoed and analysed for adherence to the protocol using the Motor Learning Strategies Rating Instrument - 20 Items[23].

Participating families will be asked to document any other therapy, health or medical interventions they receive during the study period on the participant diaries.

Exclusion during the study

All outcome data will be attempted to be collected for all enrolled participants with the exception of those who withdraw consent.

Treatment discontinuation

Participants in the intervention group or their parents may decide to stop the study intervention at any time during the study. If a participant stops the intervention for any reason, all evaluations required for the immediate and final study visit will still be offered to the participant (unless the participant formally withdraws from the study).

Data analysis plan

Sample size calculation

Results of a survey conducted by the research team indicate that approximately 25% of children with CP (GMFCS I-II) had learnt to ride a two-wheel bike in the home environment led by their parents or caregivers[8], which is likely to be the key goal of many of the study participants. Within previous studies utilising the GAS to assess the effectiveness of similar interventions in children with CP, the proportion of goals attained or participants who have reached goal attainment has been reported between 66-86% [28 35 53-55].

Given this previous data, this study is powered to find an absolute difference of 50% (from 25% in the home-program/comparison group to 75% in the intervention group) in the proportion of participants who reach goal attainment following the intervention. Assuming independent observations from individuals, a sample size of 19 in each group (38 in total) would be required to identify a difference in proportions of 50% with 80% power (based on a 2-sided test with a 5% level of significance). In this study, participants in the intervention group will receive the intervention in groups. It is likely that the outcomes for participants in the same group will be correlated or clustered hence the sample size has been inflated to account for this correlation. Assuming a small intra-cluster correlation of 0.1 between individuals within a cluster, and assuming an average cluster size of five, this equates to a design effect of 1.4, hence we will need to recruit 27 participants per arm (54 participants in total) to obtain the effective sample size of 38. Finally we inflate the required sample size to allow for 10% loss to follow-up, hence we plan to recruit a total of 60 participants (approximately 30 per group).

Statistical analysis

All statistical analysis will be conducted on an intention-to-treat basis where outcome data are available using STATA statistical software version 14[56]. Descriptive statistics will be used to characterise each group. Logistic regression will be used to assess the effect of providing the novel task-specific intervention compared to the parent-led home program on the primary outcome, bike-specific goal attainment, adjusted for site as used in the randomisation process. Logistic regression will also be used to compare secondary binary outcomes between each group and linear regression will be used to compare secondary continuous outcomes between groups.

All analyses will be conducted using mixed effects models including a random effect to allow for the clustering of participants within therapy groups in the intervention

arm. As a secondary analysis, all analyses will be repeated using a per-protocol analysis. In this analysis participants in the intervention group who discontinued the intervention prior to completing the three day program will be excluded from the analysis.

Participants will also be excluded from per-protocol analysis in either treatment group if any of the following protocol violations occur following randomisation and during the intervention and follow up periods

- Botulinum Toxin-A injections to the lower or upper limbs
- Musculoskeletal surgery or other major surgery that may affect their physical ability
- Insertion of an intrathecal baclofen pump
- Occupational therapy or physiotherapy related to training two-wheel bike skills other than the intervention or comparison group protocols

The economic appraisal will be conducted from a societal perspective. Cost-consequence analysis, including cost-effectiveness analysis and cost-utility analysis, will be carried out by comparing the incremental cost with the incremental benefit. The cost-effectiveness analysis will compare the costs to the primary and secondary outcomes demonstrating significance, and the cost-utility analysis will compare the costs to the outcomes as measured by the CHU-9D[52]. The costs associated with resources and time used for each group will be assessed and compared.

Handling of missing data

Prior to analysis, the amount of missing data will be explored, along with a comparison of distribution of key variables in individuals with and without missing data. If there is a reasonable amount of missing data and the data summaries suggest that the data are missing at random then all analyses will be presented following multiple imputation for missing data using baseline variables as auxiliary variables. Complete case analysis will also be conducted and reported. In the case there is little missing data, a complete case analysis will form the primary analysis.

ETHICS AND DISSEMINATION

This study was granted multisite approval by the Human Research and Ethics Committee at the Royal Children's Hospital (#36209). The trial is registered with the U.S. National Institutes of Health (NCT03003026) and recruitment is ongoing.

Data collected as part of this study will be entered and stored in electronic format on a REDCap secure, web-based database[57]. All other relevant electronic and paper data files will be stored securely and accessible only to study investigators. Participant confidentiality and privacy will be strictly held in trust by all study personnel.

Given the low risk nature of trial, a data monitoring committee is not required. Adverse events (AEs) will be recorded from the time the participant signs the informed consent form until the end of the last study visit. Any serious adverse event

occurring in a study participant will be reported to all involved ethics committees within 72 hours of occurrence.

This study is being completed as part of RT's Doctor of Philosophy (PhD – physiotherapy) at the University of Melbourne. It will form a major part of her thesis. The results of this study will submitted to peer-reviewed journals and presented to national and international conferences. Participating families will receive detailed summaries of the results of the study and a brief summary of the results will be distributed through the VCPR bi-annual newsletter and the CRE-CP e-newsletter/website.

SIGNIFICANCE

This study will contribute to the evidence base regarding the effectiveness of approaches to training bike skills in children with CP for attaining bike specific goals. Further, the range of secondary outcomes will allow for assessment of the effect of training bike skills on a range of meaningful outcomes for children and their families. The results of the economic evaluation will be used for policy and decision making.

INVESTIGATOR CONTRIBUTIONS

All named investigators contributed to the design of this trial protocol, to drafting and revising the manuscript and have approved this version for submission. Lead investigator Rachel Toovey is responsible for all aspects of study conduct with a particular focus on study oversight, recruitment, clinician training, reporting of adverse events, conducting study visits, outcome assessment, data management, and statistical methods. Dr Adrienne Harvey, A/Prof Jennifer McGinley and A/Prof Alicia Spittle are responsible for selected study procedures (including randomisation allocation) and study oversight. A/Prof Katherine Lee has contributed to statistical methods and will be involved in interpretation of the results. Dr Sophy Shih will contribute to economic appraisal. Rachel Toovey will lead the dissemination and translation of results, with contributions from all investigators.

ACKNOWLEDGEMENTS

We thank Frances Wright (parent advisor), Prof Andrew Davidson (Director, Melbourne Children's Trials Centre), A/Prof Adam Scheinberg, A/Prof Barry Rawicki (VPRS), Dr Sue Reid (Manager, VCPR) and Prof Dinah Reddihough (Murdoch Children's Research Institute) for their contributions to this protocol and in-kind support of this study.

REFERENCES

1. Stanley F, Blair E, Alberman E. How common are the cerebral palsies? Cerebral Palsies: Epidemiology and Causal Pathways. London: MacKeith Press 2000:22-29.
2. Bax M, Goldstein M, Rosenbaum P, et al. Proposed definition and classification of cerebral palsy. *Dev Med Child Neurol* 2005;47:571-76.

3. Bjornson K, Belza B, Kartin D, et al. Ambulatory physical activity performance in youth with cerebral palsy and youth who are typically developing. *Phys Ther* 2007;87:248-57.

4. Fernandes R, Sansecso A. Early physical activity promotes lower prevalence of chronic disease in adulthood. *Hypertens Res* 2010;33(9):926-31.

5. Novak I, McIntryre S, Morgan C, et al. A systematic review of interventions for children with cerebral palsy: state of the evidence. *Dev Med Child Neurol* 2013;55(10):885-910.

6. Australian Bureau of Statistics. Children's Participation in Cultural and Leisure Activities http://www.abs.gov.au/ausstats/abs@.nsf/Products/4901.0~Apr+2012~Main+Features~Recreational+activities?OpenDocument 2012 [accessed 18 February 2016 2016.

7. Palisano R, Rosenbaum P, Walter S, et al. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214-23.

8. Toovey R, Reid S, Harvey A, et al. Ability of ambulatory children with cerebral palsy to ride a bike and age at skill acquisition. *Dev Med Child Neurol* 2017;59(4):395-401.

9. Demuth SK, Knutson LM, Fowler EG. The PEDALS stationary cycling intervention and health-related quality of life in children with cerebral palsy: a randomized controlled trial. *Dev Med Child Neurol* 2012;54(7):654-61. doi: http://dx.doi.org/10.1111/j.1469-8749.2012.04321.x

10. Fowler EG, Knutson LM, Demuth SK, et al. Pediatric endurance and limb strengthening (PEDALS) for children with cerebral palsy using stationary cycling: a randomized controlled trial. *Phys Ther* 2010;90(3):367-81.

11. Siebert KL, DeMuth SK, Knutson LM, et al. Stationary cycling and children with cerebral palsy: case reports for two participants. *Phys Occup Ther Pediatr* 2010;30(2):125-38. doi: http://dx.doi.org/10.3109/01942630903578399

12. Sakzewski L, Ziviani J, Boyd R. Efficacy of Upper Limb Therapies for Unilateral Cerebral Palsy: A Meta-analysis. *Pediatrics* 2014;133(1):e175-204.

13. French B, Thomas LH, Leathley MJ, et al. Repetitive task training for improving functional ability after stroke. *Cochrane Database Syst Rev* 2007;17(4) doi: 10.1002/14651858.

14. Hubbard IJ, Neilson C, Carey LM. Task-specific training: evidence for and clinical practice. *Occup Ther Int* 2009;16(3-4):175-89.

15. Bar-Haim S, Harries N, Nammourah I, et al. Effectiveness of motor learning coaching in children with cerebral palsy: a randomized controlled trial. *Clin Rehabil* 2010;24(11):1009-20. doi: http://dx.doi.org/10.1177/0269215510371428

16. Thelen E, Smith L. Theoretical Models of Human Development (chapter 6). In: John Wiley and Sons, ed. Dynamic Systems Theories. London2007.

17. Shumway-Cook A, Woollacott M. Motor Control: Translating Research into Clinical Practice (Fourth Edition). Baltimore, MD: Lippincott Williams & Wilkins 2012.

18. Bleyenheuft Y, Arnould C, Brandao MB, et al. Hand and Arm Bimanual Intensive Therapy Including Lower Extremity (HABIT-ILE) in Children With

Unilateral Spastic Cerebral Palsy: A Randomized Trial. *Neurorehabil Neural Repair* 2015;29(7):645-57.

19. Kumban W, Amatachaya S, Emasithi A, et al. Effects of task-specific training on functional ability in children with mild to moderate cerebral palsy. *Dev Neurorehabil* 2013;16(6):410-7.
20. Toovey R, Rawicki B, Harvey A. Outcomes of a goal directed intensive bicycle skills group program for children with cerebral palsy: a pilot case series. Australasian Academy of Cerebral Palsy and Developmental Medicine Conference. Adelaide, Australia: Dev Med Child Neurol, 2016:60-61.
21. Roberts G, Howard, K. Spittle A.J., Brown, N.C., Anderson, P.J., and Doyle, L.W. . Rates of early intervention services in very preterm children with developmental disabilities at age 2 years. *Journal of Paediatrics and Child Health* 2007 doi: doi:10.1111/j.1440-1754.2007.01251.x
22. Kiresuk T, Sherman R. Goal attainment scaling: a general method of evaluating comprehensive mental health programmes. *Community Ment Health J* 1968;4:443-53.
23. Ryan J, Levac D, Wright FV. Motor learning strategies rating instrument-20 items (MLSRI-20) instruction manual. Toronto, CA: Holland Bloorview Kids Rehabilitation Hospital, 2016.
24. Thorpe DE, Valvano J. The effects of knowledge of performance and cognitive strategies on motor skill learning in children with cerebral palsy. *Pediatr Phys Ther* 2002;14(1):2-15.
25. Thomas RE, Johnston LM, Sakzewski L, et al. Evaluation of group versus individual physiotherapy following lower limb intra-muscular Botulinum Toxin-Type A injections for ambulant children with cerebral palsy: A single-blind randomized comparison trial. *Res Dev Disabil* 2016;53-54:267-78.
26. Hemayattalab R, Arabameri E, Pourazar M, et al. Effects of self-controlled feedback on learning of a throwing task in children with spastic hemiplegic cerebral palsy. *Res Dev Disabil* 2013;34(9):2884-9.
27. Lowing K, Bexelius A, Brogren Carlberg E. Activity focused and goal directed therapy for children with cerebral palsy - do goals make a difference? *Disabil Rehabil* 2009;31(22):1808-16. doi: 10.1080/09638280902822278
28. Steenbeek D. Goal attainment scaling in paediatric rehabilitation. Utrecht University, 2010.
29. Lowing K, Bexelius A, Brogren Carlberg E. Activity focused and goal directed therapy for children with cerebral palsy--do goals make a difference? *Disabil Rehabil* 2009;31(22):1808-16. doi: http://dx.doi.org/10.1080/09638280902822278
30. Lowing K, Bexelius A, Brogren-Carlberg E. Goal-directed functional therapy: a longitudinal study on gross motor function in children with cerebral palsy. *Disabil Rehabil* 2010;32(11):908-16.
31. Kuhlthau K, et al. Evidence for family-centered care for children with special health care needs: a systematic review. *Acad Pediatr* 2011;11:136-43.
32. Novak I, Cusick A, Lannin N. Occupational therapy home programs for cerebral palsy: double-blind, randomized, controlled trial. *Pediatrics* 2009;124(4):e606-14. doi: http://dx.doi.org/10.1542/peds.2009-0288

33. Palisano R. Validity of goal attainment scaling in infants with motor delays. *Phys Ther* 1993;73(10):651-58.
34. Steenbeek D, Ketelaar M, Lindeman E, et al. Interrater reliability of goal attainment scaling in rehabilitation of children with cerebral palsy. *Archives of Physical Medicine & Rehabilitation* 2010;91(3):429-35.
35. Steenbeek D, Ketelaar M, Galama K, et al. Goal attainment scaling in paediatric rehabilitation: a critical review of the literature. *Dev Med Child Neurol* 2007;49(7):550-56.
36. Toovey R, Harvey AR, McGinley JL, et al. Bike Skills Training for Children With Cerebral Palsy. US National Library of Medicine Clinical Trials Register ID: NCT03003026. ClinicalTrials.gov 2016.
37. Krasny-Pacini A, Evans J, Sohlberg M, et al. Proposed criteria for appriasing goal attainment scales used as outcome measures in rehabiliation research. *Arch Phys Med Rehabil* 2016;97:157-70.
38. Wassenberg-Severijnen J, Maas C, Custers J, et al. Standardization of the Dutch 'Pediatric Evaluation of Disability Inventory' (PEDI). Chapter 5, Pediatric Evaluation of Disability Inventory (PEDI): Calibrating the Dutch Version. Utrect University, 2005.
39. Halayko J. You Can Ride Too! An Exploration of the Guided Discovery of Two-wheeled Cycling Skills by Youth with Intellectual Disabilities. University of Alberta, 2014.
40. Custers J, et al. Discriminative validity of the Dutch PEDI. *Arch Phys Med Rehabil* 2002;83:1437-41.
41. Halayko J, Magill-Evans J, Smith V, et al. Enabling 2-wheeled cycling for youth with Down Syndrome. *Pediatr Phys Ther* 2016;28:224-30.
42. Haley SM, Coster WJ, Dumas HM, et al. Pediatric Evaluation of Disability Inventory Computer Adapative Test - Development, Standardization and Administration Manual http://www.pedicat.com.2012 [accessed July 2016.
43. Activ8 (TM) physical activity monitor https://www.activ8all.com/2015 [accessed 17 July 2016.
44. Crocker PRE, Bailey DA, Faulkner RA, et al. Measuring general levels of physical activity: preliminary evidence for the Physical Activity Questionnaire for Older Children. *Med Sci Sports Exerc* 1997;29(10):1344-9.
45. Gorter J, et al. Accelerometry: A feasible method to quantify physical activity in ambulatory and nonambulatory adolescents with cerebral palsy. *Int J of Ped* 2012
46. Janz KF, Lutuchy EM, Wenthe P, et al. Measuring Activity in Children and Adolescents Using Self-Report: PAQ-C and PAQ-A. *Medicine & Science in Sports & Exercise* 2008;40(4):767-72.
47. Harter S, Pike R. The Pictoral Scale of Percevied Competence and Social Acceptance for Young Children: Manual https://portfolio.du.edu/SusanHarter/page/44342: University of Denver; 1983 [accessed July 2016.
48. Harter S. Self-Perception Profile for Children https://portfolio.du.edu/SusanHarter/page/44210: Unviersity of Denver; 2012 [accessed July 2016.

49. Harter S. Self-Perception Profile for Adolescents https://portfolio.du.edu/SusanHarter/page/44210: University of Denver; 2012 [accessed July 2016.
50. Barnett LM, Ridgers ND, Zask A, et al. Face validity and reliability of a pictorial instrument for assessing fundamental movement skill perceived competence in young children. . *J Sci Med Sport* 2015;18:98-102.
51. Barnett LM, Vazou, S., Abbott, G., Bowe, S.J., Robinson L.E., Ridgers N.D., Salmon, J. . Construct validity of the pictorial scale of Perceived Movement Skill Competence. *Psychol Sport Exerc* 2016;22:294-302.
52. Stevens KJ. Assessing the performance of a new generic measure of health related quality of life for children and refining it for use in health state valuation. *Appl Health Econ Health Policy* 2011;9(3):157-69.
53. Ahl LE, Johansson E, Granat T, et al. Functional therapy for children with cerebral palsy: an ecological approach. *Dev Med Child Neurol* 2005;47:613-19.
54. Lowing K, Bexelius A, Brogren Carlberg E. Activity focused and goal directed therapy for children with cerebral palsy-do goals make a difference? *Disabil Rehabil* 2009;31(22):1808-16.
55. Sorsdahl AB, Moe-Nilssen R, Kaale HK, et al. Change in basic motor abilities, quality of movement and everyday activities following intensive, goal-directed, activity-focused physiotherapy in a group setting for children with cerebral palsy. *BMC Pediatr* 2010;10:26.
56. StataCorp. Stata Statistical Software: Release 14.: College Station, TX, 2015.
57. Harris P, Taylor R, Thielke R, et al. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42(2):377-81.

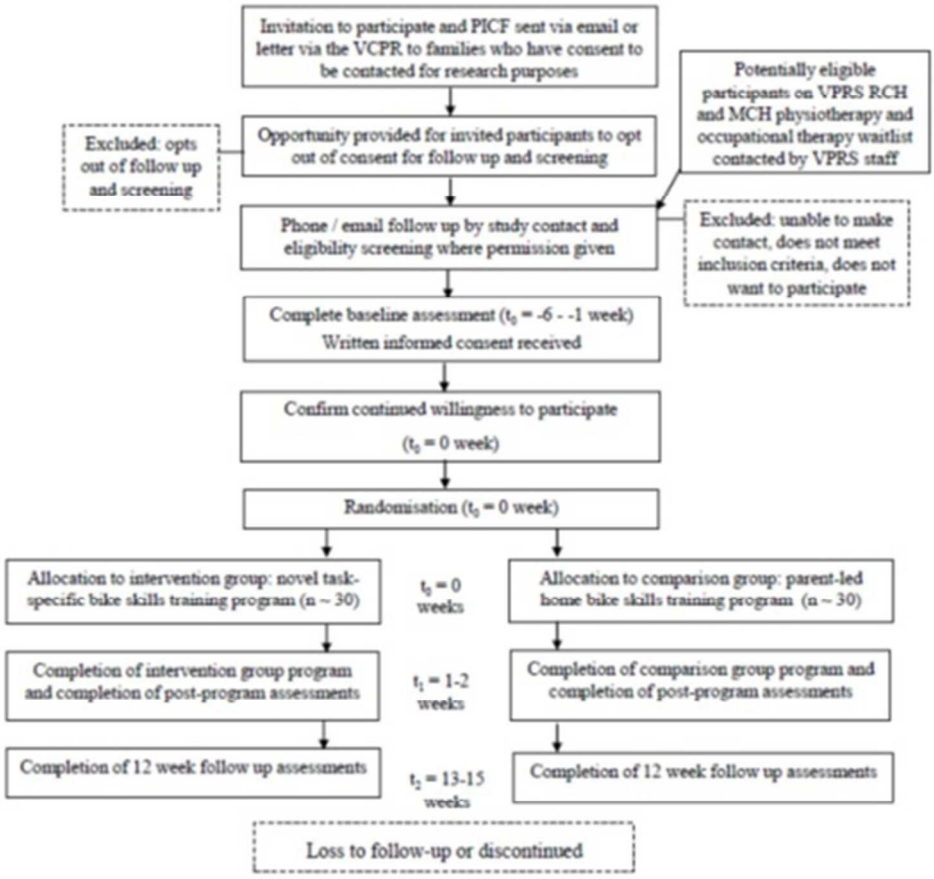

Figure 1: Study timeline

49x44mm (300 x 300 DPI)

Appendix 1: Schedule of assessments

VARIABLES		STUDY PERIOD			
	Initial Eligibility Screen	Baseline Assessment	Allocation	Follow up study visits	
TIME POINT**	*t_{-1}*	t_{-1} = -6 to -1 weeks	t_0 = 0	*t_1 = 1-2 weeks*	*t_2 = 13-15 weeks*
Confirmed CP	X				
GMFCS	X	X (Confirm)			
Age	X				
Intellectual ability	X				
Healthy care giver available	X				
Live in Victoria / near border	X				
Appropriate bike and helmet	X				
Medical clearance	X				
BonT-A injections or surgery (including insertion of baclofen pump) in last 6 months	X	X		X	X
No other bike related therapy during intervention and follow up period				X	X
Informed Consent		X			
Allocation			X		
Topography and motor type		X			
Manual Ability Classification Scale (MACS)		X			
Previous bike riding practice		X			
Parent rated importance of bike skills goal attainment		X			
Parent bike skills competence and interest		X			
Parent social risk questionnaire		X			
Goal attainment (GAS)		X		X	X
Two-wheel bike skills (PEDI-NL & Cycling skills checklist)		X		X	X
Functional skills (PEDI-CAT)		X		X	X

Physical activity behaviour (accelerometer & PAQ-C)		X			X
Self-perception (SPP-C/A)		X		X	X
Self-perceived bike riding competence		X		X	X
Cost Utility (CHU -9D)		X		X	X
Attendance and involvement in intervention group				X	X
Practice in intervention and comparison group				X	X
Child involvement in intervention and comparison group training				X	X
Other therapy or medical interventions				X	X
Adverse events		X		X	X

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Abstract p1, protocol p1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract p1, protocol p14, 18
	2b	All items from the World Health Organization Trial Registration Data Set	Abstract p1
Protocol version	3	Date and version identifier	Protocol p1
Funding	4	Sources and types of financial, material, and other support	Protocol p1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Abstract p1, protocol p1
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Protocol p15
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Abstract p2, protocol p4
	6b	Explanation for choice of comparators	Protocol p2, 9-10
Objectives	7	Specific objectives or hypotheses	Protocol p5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Abstract p2, Protocol p5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Protocol p5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Protocol p6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Protocol p8-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Protocol p14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Protocol p12, 15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Protocol p14

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Protocol p10-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1, Appendix 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Protocol p13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Protocol p6-7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Protocol p8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Protocol p8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Protocol p8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Protocol p8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Protocol p8
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Protocol p10-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Protocol p12-13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Protocol p14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Protocol p13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Protocol p13-14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Protocol 13-14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Protocol p14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Protocol p14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Protocol p14-15
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Protocol p1, 14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Protocol p14-15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Protocol p7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Protocol p14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Protocol p1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Abstract p2
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not attached

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Bike skills training for children with cerebral palsy: protocol for a randomised controlled trial

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019898.R1
Article Type:	Protocol
Date Submitted by the Author:	28-Nov-2017
Complete List of Authors:	Toovey, Rachel; Murdoch Childrens Research Institute, Developmental Disability and Rehabilitation Research; University of Melbourne, Physiotherapy Harvey, Adrienne; Murdoch Childrens Research Institute, Developmental Disability and Rehabilitation Research; The Royal Children's Hospital, Melbourne, Neurodevelopment and disability McGinley, Jennifer; University of Melbourne, Physiotherapy Lee, Katherine; Murdoch Children's Research Institute, Melbourne Children's Trials Centre; University of Melbourne Shih, Sophy; Deakin University, Deakin Population Health Spittle, Alicia; University of Melbourne, Physiotherapy; Murdoch Childrens Research Institute, Victorian Infant Brain Studies
Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Neurology, Rehabilitation medicine, Sports and exercise medicine
Keywords:	Cerebral palsy, Physical activity, Participation, Children, REHABILITATION MEDICINE

BIKE SKILLS TRAINING FOR CHILDREN WITH CEREBRAL PALSY: PROTOCOL FOR A RANDOMISED CONTROLLED TRIAL

Investigator names:

Rachel Toovey[1, 2, 3] Adrienne R. Harvey[2, 4, 5], Jennifer L. McGinley[1], Katherine J. Lee [5, 6, 7], Sophy T.F. Shih[8], Alicia J. Spittle[1, 9]

Institutional affiliations:

1. Department of Physiotherapy, University of Melbourne, Melbourne, Australia
2. Developmental Disability and Rehabilitation Research, Murdoch Children's Research Institute, Melbourne, Australia
3. Victorian Paediatric Rehabilitation Service, Monash Children's Hospital, Melbourne, Australia
4. Neurodevelopment and Disability, The Royal Children's Hospital, Melbourne, Australia
5. Department of Paediatrics, University of Melbourne, Melbourne, Australia
6. Clinical Epidemiology and Biostatistics Unit, Murdoch Children's Research Institute, Melbourne, Australia
7. Melbourne Children's Trials Centre, Melbourne Children's Campus, Melbourne, Australia
8. Deakin Health Economics, Centre for Population Health Research, Deakin University, Geelong, Australia
9. Victorian Infant Brain Studies, Murdoch Children's Research Institute

Corresponding author: A/Prof Alicia J. Spittle. Department of Physiotherapy, University of Melbourne, Alan Gilbert Building, 161 Barry St, Carlton 3053. Email: aspittle@unimelb.edu.au

Funding: This work was supported by a Physiotherapy Research Foundation Seeding Grant (S16-007), an Australian Government Research Training Program Scholarship (RT), National Health Medical Research Council (NHMRC) Centre of Research Excellence in Cerebral Palsy ID 1057997 (RT, ARH. SS), Centre of Research Excellence in Newborn Medicine ID 1060733 (AJS), NHMRC Career Development Fellowship ID 1053767 (AJS), Melbourne Children's Campus Clinician Scientist Fellowship (ARH), Murdoch Children's Research Institute (RT, ARH and KJL) and the Victorian Government's Operational Infrastructure Support Program.

Completing interests: The investigators have no conflicts of interest to declare. The main funding body of this trial (Physiotherapy Research Foundation) has had no role in the study design or procedures and will have no role in reporting and associated publications.

ABSTRACT

Introduction: Two-wheel bike riding can be a goal for children with cerebral palsy (CP) and a means of participating in physical activity. It is possible for some children with CP to ride a two-wheel bike, however, currently far fewer can ride compared with their typically developing peers. Evidence supports training targeted towards goals of the child with CP and their family; yet there is little evidence to guide best-practice bike skills training. Task-specific training may lead to attainment of two-wheel bike specific goals. This study aims to determine if a novel task-specific approach to training two-wheel bike skills is more effective than a parent-led home program for attaining individualised two-wheel bike specific goals in independently ambulant children with CP aged 6 -15 years.

Methods and Analysis: Sixty eligible children with CP (Gross Motor Function Classification System levels I-II) aged 6 – 15 with goals relating to riding a two-wheel bike will be randomised to either a novel task-specific centre-based group program (intervention) or a parent-led home-based program (comparison), both involving a one week intervention period. The primary outcome is goal attainment in the week following the intervention period (T1). Secondary outcomes include; goal attainment and participation in physical activity at three months post intervention (T2) and bike skills, attendance and involvement in bike riding, self-perception and functional skills at T1 and T2. Economic appraisal will involve cost-effectiveness and cost-utility analyses. Adherence of clinicians and parents to the intervention and comparison protocols will be assessed. Linear and logistic regression will be used to assess the effect of the intervention, adjusted for site as used in the randomisation process.

Ethics and dissemination: This study was approved by the Human Research and Ethics Committees at the Royal Children's Hospital (#36209). Results will be disseminated via peer-reviewed publications and conference presentations.

Registration: NCT03003026; pre-results, recruitment ongoing.

STRENGTHS AND LIMITATIONS

- To our knowledge, this will be the first adequately powered randomised controlled trial to evaluate the effectiveness of a novel task-specific bike skills training program for attaining bike-specific goals in children with cerebral palsy
- The range of secondary outcomes will allow for assessment of the effects of training bike skills on a range of activity and participation outcomes
- Assessment of fidelity will enable evaluation of the extent to which clinicians and families adhere to the intervention and comparison group protocols
- The economic appraisal will be useful for future policy and decision-making
- Due to the nature of the intervention, clinicians delivering the interventions and participants will not be blind to allocation

Key words

Cerebral palsy

Physical activity

Participation

Children

INTRODUCTION

Cerebral Palsy (CP) is the most common cause of childhood physical disability affecting one in five hundred births[1]. It is a group of disorders of the development of movement and posture, causing activity limitations that are attributed to non-progressive disturbances occurring in the developing foetal or infant brain[2]. Children with CP participate less in physical and recreational activities than their typically developing peers[3], putting them at increased risk of poor health and disease in adulthood[4]. Effective means of engaging children with CP are required to improve physical activity patterns in this population, and evidence supports training targeted towards goals of the child and their family[5]. Bike riding is a common activity for families[6] and may be an effective means of involving ambulant children with CP in physical activity that is enjoyable and meaningful to them.

The Gross Motor Function Classification System (GMFCS)[7] uses five levels (I-V) to classify children with CP according to their level of motor function. Children classified as levels I-II are independently ambulant with or without hand-held devices. Far fewer ambulant children with CP (GMFCS I-II) can ride a two-wheel bike at any given age compared to their typically developing peers, and if they do, they learn later in life. However, it is possible for children with CP at GMFCS levels I and II to learn to ride and the majority who do so, learn at home with their parents[8].

Physiotherapists and occupational therapists routinely implement training to improve motor skills in children with CP. However, there is very little specific evidence to guide best practice in training of bike riding skills. The studies that do exist specific to children with CP have been conducted on stationary bikes[9-11] with no evidence to suggest this translates to riding a two-wheel bike in the community. Further, the current practices of Australian physiotherapists and occupational therapists for training two-wheel bike skills in children with CP are not well understood. Importantly, there does not appear to be a standard or usual care.

The development and testing of approaches to training bike skills is required to provide clinicians and families with evidence-based guidance when working with children with CP with two-wheel bike specific goals. Strong evidence exists for task-specific training to improve general upper limb function in this population[5 12] and gross motor skills in adults following stroke[13]. Task-specific training involves practice of context-specific tasks where the intervention focuses on the skills needed for a task(s)[14]. It is informed by principles of motor learning[15] and dynamic systems theory[16] and involves a dynamic interaction between the task, the child and the environment to achieve a motor skill in a task-specific context[17]. Evidence for task-specific training to improve gross motor skills in ambulant children with CP exists[18 19], but is currently limited by poor study methodology and intervention heterogeneity. An intensive task-specific approach to training bike skills has seen promising outcomes in a group setting at the two main paediatric rehabilitation settings in Victoria, Australia demonstrated through results from a small pilot case series (n=5)[20].

Whilst this clinical evidence supports the safety and feasibility of task-specific training in bike riding in a group setting, an adequately powered study with a comparison group is required to ascertain the effectiveness of such an approach.

Objectives

The primary objective of this study is to determine if a novel task-specific approach to training bike skills is more effective than a parent-led home program in ambulant children with CP (GMFCS I-II) aged 6 - 15 years, for attaining individualised two-wheel bike specific goals immediately following the intervention period (T1).

The secondary objectives of this study are:

1. To determine if a novel task-specific approach to training bike skills is more effective compared to a parent-led home program in children with CP (GMFCS I-II) aged 6 - 15 on
   a. Goal attainment at three months following the intervention (T2)
   b. Acquiring and retaining two-wheel bike skills at T1 and T2
   c. Functional skills at T1 and T2.
   d. Physical activity behaviour at T2
   e. Self-perception at T1 and T2
   f. Self-perceived bike riding competence at T1 and T2
2. To compare attendance and involvement in bike skills training between the intervention and comparison groups during the intervention and follow up periods
3. To conduct an economic appraisal, involving assessment of quality of life, of the intervention compared to the comparison program
4. To examine clinician and parent fidelity with delivery of both group protocols

METHODS AND ANALYSIS

Design

Assessor-blinded, parallel group, randomised controlled, multicentre, superiority trial comparing a novel task-specific approach to a parent-led home program for training bike skills. This study involves a one week intervention period and three month follow up period (Figure 1).

Setting

The study will be conducted through the Victorian Paediatric Rehabilitation Service (VPRS: a state wide rehabilitation service for children with rehabilitation goals including children with CP) at the Royal Children's Hospital and the Monash Children's Hospital in Melbourne, Australia.

Participants

Sixty participants will be recruited from the Victorian Cerebral Palsy Register (VCPR: a register of children with CP who were born in Victoria or receive health services in Victoria) and the VPRS. Approximately 30 children will be randomised to the intervention group and 30 children will be randomised to the comparison group (Figure 1). Each participant must meet all of the inclusion criteria and none of the exclusion criteria to be enrolled in this study (Table 1).

Table 1: Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• Is between 6 - 15 years old at the time of randomisation • Has CP as determined by the VCPR or in writing from the child's general practitioner or paediatrician if not on the VCPR • Is independently ambulant without aids (GMFCS I-II) • Has goals related to improving two-wheel bike skills • Has a primary caregiver available to participate in the intervention • Has a legally acceptable representative capable of understanding the informed consent document and providing consent on the participant's behalf • Lives in Victoria or close to the Victorian border in New South Wales and receives health services in Victoria • Has access to an appropriately sized two-wheel bike and helmet • Has medical clearance to participate in the study from the child's general practitioner, paediatrician or paediatric specialist • Participant and primary caregiver able to understand English	• Has a moderate to severe intellectual impairment • Has a dual diagnosis with another developmental disability or medical condition that may impact on their ability or safety to train two-wheel bike skills • Had musculoskeletal surgery, or other major surgery including insertion of a baclofen pump that may affect their physical ability in the 6 months prior to randomisation • Had Botulinum toxin-A injections to the lower limbs and/or upper limbs in the six months prior to randomisation

Recruitment procedures

Participants will be identified and recruited through the VCPR and the VPRS at the Royal Children's Hospital and Monash Children's Hospital. The study will also be

advertised on the National Health and Medical Research Council (NHMRC) Centre of Research Excellence in Cerebral Palsy (CRE-CP) newsletter and website.

Victorian Cerebral Palsy Register

Within this register, it is recorded whether parents or primary care givers have consented to being contacted for research purposes. Invitations to participate in the study will be sent by VCPR staff to potentially eligible participants whose parents/primary care givers have provided consent by email or letter including a full participant information and consent form. Families will have the opportunity to contact the VCPR to request that their contact details not be passed onto the study team for follow up and screening for eligibility which will occur by email and phone.

The Victorian Paediatric Rehabilitation Service

Waitlists for services and clinics at VPRS sites at The Royal Children's Hospital and Monash Children's Hospital, will also be used to identify potentially eligible participants. A VPRS clinician will contact the parents of potentially eligible participants as per respective VPRS site physiotherapy waitlists. Potentially eligible participants who attend VPRS clinics at both hospitals during the recruitment period but are not yet on the respective VPRS physiotherapy waitlists will also be identified by VPRS clinicians. Interested families will be given the study contact's details or permission will be sought by the VPRS clinicians to pass their contact information on to the study contact for screening and follow up.

The Centre for Research Excellence in Cerebral Palsy website and e-newsletter

An advertisement inviting eligible families to participate in the study will be posted on a parent, clinician and researcher website for the management and treatment of CP (http://www.cre-cp.org.au) and in the website's e-newsletter during the recruitment period.

Baseline study visit

Eligible participants will be enrolled in the study at the baseline (T0) assessment visit up to six weeks prior to the intervention period. Written informed consent will be obtained prior to performing any assessments and randomisation by Principal Investigator or trained outcomes assessor. The following will be collected at the T0 assessment (see also Appendix 1):

- Age, intellectual impairment (if any) and description of the CP including: topography, motor type, GMFCS level and Manual Ability Classification System level
- Previous time spent practicing bike skills on average per week or month since commencement of bike skills practice
- Parent rated importance of their child attaining their goals, competence of their own bike skills and family interest in bike riding on a five point scale

- Family social risk as measured by a questionnaire comprised of six questions regarding social status including family structure, education of primary caregiver, occupation of primary income earner, employment status of primary income earner, language spoken at home and maternal age at birth[21]
- Goals will be set by the child, parent and outcomes assessor together using the Goal Attainment Scale (GAS)[22]
- Baseline data for secondary outcomes will be collected including: two wheel bike skills, functional skills, physical activity behaviour, self-perception, self-perceived two-wheel bike riding competence and health-related quality of life as assessed by the measures detailed below under "Primary and secondary outcome measures."

Randomisation and blinding

A statistician not directly involved in the study will prepare the randomisation schedule using computer-generated block randomisation with variable block sizes. Randomisation will be stratified by site. The statistician will generate opaque, numbered, sealed envelopes according to the randomisation schedule. In the week prior to the intervention period the participant will be allocated a sequential study number within the appropriate strata. Participants will then be randomised by a study investigator not involved in assessment procedures who will open the envelopes and inform participants of their allocation via phone or email. Participants who are already known to either site will be randomised within that site, otherwise families will be randomised within a site based on family preference or home location. The outcome assessors will be blind to group allocation but it will not be possible to blind the treating clinicians or participants.

Details of the intervention and comparison

The intervention: Novel task-specific bike skills training program

Participants randomised to the intervention group will participate in a novel bike skills training program conducted over three consecutive days, with a further four days for practicing the learnt skills at home (seven-day intervention period). This approach involves seven key components:

1. Task-specific: Training will be informed by the dynamic systems theory and principles of motor learning. The dynamic interaction between systems including the task, the child and the environment is considered to achieve motor skills in a task-specific context [16]. Each of these systems is considered at the stages of the motor learning process. Initially new motor tasks are scaffolded, so that the participant will always actively complete at least part of the task. This may involve task demonstration or physical guidance. As performance improves, the task and/or environment in altered to encourage problem solving and increase the motor challenge. This may include modifying the bike (e.g. seat height, location of the brakes, basic straps for hand or feet) and reducing the physical guidance in order to achieve each progression of the skill/s. Once a motor skill is acquired, variability and randomness of practice in terms of task

difficulty and environmental challenge will be introduced to increase the complexity and generalisability of the skill[23]. Overall practice will be repetitive, progressive, variable and favour whole skill practice rather than part practice[23]. The amount and type of feedback from the trainer will be guided by participant preference, and will focus on knowledge of results or performance for each new skill [24], for example getting on and off the bike. Participants will utilise their own two-wheel bike without training wheels and helmet where possible. Cones or markers will be used as visual cues for skill practice.

2. Group-based: Training will be delivered to groups of up to six participants. There is evidence to suggest group-based rehabilitation programs improve functional skills, self-perceived performance and cost-effectiveness of treatment as much, or more than individual therapy [25].
3. Clinician-mediated: Each program will be conducted by at least one physiotherapist and one other clinician (physiotherapist, occupational therapist or allied health assistant). There will be a minimum ratio of one clinician to three child participants in each group. All clinicians will be employed by VPRS and will undertake six to eight hours training in the intervention protocol in the four months prior to delivering the intervention. The same two clinicians will lead the three days of each program.
4. Intensive: Each program will run for two hours per day over three consecutive days during one week of the school holiday period. This intensity is supported by motor learning literature, in particular the benefits of repetitive practice in the skill acquisition phase[26]. This intensity allows for repetitive practice[18], including repetitive practice in the home environment following the program and has been supported by parent evaluation of the intensive program delivered as part of the pilot case series[20]. Breaks from physical activity will be offered at least every 30 minutes and families can request additional rests. Participants will also be given a home program of one to three bike skills practice exercises following each session and encouraged to practice these up to 30 minutes per day during the week-long intervention period and three to five bike skills to practice when able in the three month follow up period.
5. Goal-directed: Evidence suggests interventions that are goal-directed improve gross motor function more than those that are not[27]. Goal setting is a key component of paediatric rehabilitation and has been well established in the literature [28]. The Goal Attainment Scale (GAS) will be used as an outcome measure and as a process for setting goals related to bike skills training. Clinicians delivering the intervention will be aware of each participant's goals, which will be used to provide individualised opportunities for problem solving and drive the movements required to meet the task demands[29 30].
6. Parent or caregiver involvement: At least one parent or caregiver will be required to attend each session of the program. Parent involvement and education is recognised as a key component in family-centred practice[31]. It facilitates a partnership between the clinician and parent towards achieving the child's goal. Parents will be coached by the clinician during the three-day intervention regarding approaches to motor learning, including gradually increasing the difficulty of the task whilst ensuring this intersects with success. Parents will be provided verbal guidance regarding strategies and safety of practice in the home environment[23].

7. Ecological setting: When possible the program will be conducted in outdoor recreation or community reserves at or in close proximity to the rehabilitation service. This aligns with dynamic systems theory and task-specific training in terms of the role the environment has in promoting motor learning. Different surfaces and gradients will be available to individualise the environment based on each participant's stage of motor learning and to promote successful problem solving. All program settings will be conducted away from roads and busy public spaces. Participants will be encouraged to practice outside of the program in similar environments and advised to avoid practice on roads, busy bike paths or other risky environments during the intervention and follow up periods.

The comparison: Parent-led home bike skills training program

Current bike skills training for children with CP is not well understood. Given the lack of specific evidence, current practice is not likely to be uniform in approach, dosage or setting. Whilst the majority of ambulant children with CP (GMFCS I-II) are currently not able to ride a two-wheel bike, many of those who can ride learnt in informal settings with their families[8]. There also is evidence to support home-based therapy programs involving parent education for goal attainment in children with CP [5] [32]. Given this, it seemed appropriate that the comparison group for the intervention was a parent-led, home-based program.

Participants randomised to the comparison group will receive written general information on training bike skills either in person or via email dependent on consenting and baseline assessment location. Families will receive this information at the start of the one-week period of training during the school holidays. Parents will be encouraged to work with their child on two-wheel bike skills goals guided by the written information (available on request). This information involves:

1. Intensity: Families will be encouraged to practice at least 30 - 45 minutes on each of the seven days of the one-week period.
2. Safety: Families will be encouraged to practice in settings away from roads and busy public spaces. They will also be advised to perform a risk assessment of the location prior to commencing. Information on appropriate weather and adequate hydration will also be included.
3. Appropriate bike and helmet fit: Information regarding fitting the bike and helmet to the child for skill development, safety and potentially useful modifications will be provided.

A trained VPRS physiotherapist will also telephone families in the comparison group between three to five days into training period. The purpose of this phone call will be to inquire about how the family is managing with the training program and to offer general advice regarding practice for the remaining two-four days of the training period.

Primary and secondary outcome measures

Outcomes will be measured in the week following (T1) and three months (12-14 weeks) following (T2) the intervention period (Appendix 1). Outcomes will be assessed by the Principal Investigator (RT) or a physiotherapist trained in the outcomes assessment, both blinded to group allocation.

The primary outcome, goal attainment at T1, will be measured using the GAS, a criterion referenced tool for individualized and collaborative goal setting between the child, family and clinician[22 28 33]. The GAS is commonly used in rehabilitation for children with CP because it is valid[33], reliable and responsive[34] in this heterogeneous population. The GAS will be facilitated by the blinded outcomes assessors, trained in administering the GAS. Two to three individualized and measurable two-wheel bike specific activity or participation goals per participant will be set at the baseline visit (T0). Six potential outcomes will be specified for each goal: -3 (deterioration), -2 (equal to start), -1 (less than expected), 0 (expected), 1 (somewhat more than expected), 2 (much more than expected).[35] Children aged 8 – 15 will lead the goal setting at T0 and scoring of goal attainment at T1, whilst children aged 6 – 7 will complete the process with their parent and clinician. The primary outcome, goal attainment, is defined as attainment of at least one goal to an expected (score of zero) or greater level. While varied interpretations of goal attainment have been used, including averaging the number of goals achieved, recent literature in rehabilitation suggests that the chosen definition reflects a clinically relevant change and allows for appropriate statistical analysis, in that it is not treated as a continuous variable[35 36 37] .

The secondary outcomes will be assessed as follows:

- Goal attainment at T2 measured using the GAS[28]
- Bike skills acquisition and retention measured using the subscale items related to bike skills in the mobility domain of the functional skills in the Dutch calibration of Paediatric Evaluation of Disability Inventory (PEDI-NL)[38] and the Cycling Skills Checklist[39] at T1 and T2. The PEDI is a commonly used scale to measure functional status across the domains of self-care, mobility and social function in children with disability. As part of its calibration for use in the Netherlands, a subscale was added to the mobility domain involving four levels of bike riding skill. The PEDI-NL has good content and discriminative validity and is reliable in children with disabilities[40]. The Cycling Skills Checklist is a 20 item checklist of beginner bike skills where a score out of five is given for each skill. The maximum score for the highest level of bike skills is 100. It has not been validated in children with CP however has been used in research with children with Down syndrome[41].
- Functional skills measured using the PEDI-CAT[42] (computer adaptive test) at T1 and T2. The PEDI-CAT is a comprised of a comprehensive item bank of 276 functional activities acquired throughout infancy, childhood and adolescence. The PEDI-CAT measures function in four domains: (1) Daily Activities; (2) Mobility; (3) Social/Cognitive, and (4) Responsibility. It is valid and reliable for use in parents of children with all ages with CP. The Content-Balanced version of the PEDI-CAT will be used.

- Physical activity behaviour measured using a triaxial accelerometer[43] and the Physical Activity Questionnaire for Children (PAQ-C)[44] at T2. Accelerometry is a feasible, reliable and validated method of measuring activity in children and young people with CP[45]. The Activ8 ™ will be used as it is able to distinguish cycling as a different type of physical activity from walking, running, standing and sitting[43]. The Activ8 ™ will be worn by each participant for 7 days at T0 and at T2. The Physical Activity Questionnaire for Children (PAQ-C) is a valid and reliable[46] self-report 7-day recall assessment of physical activity in children aged 8-20 years.
- Overall self-perception measured with the Pictorial Scale of Perceived Competence and Social Acceptance for Young Children[47] (ages 6-7 years) or the Self Perception Profiles for Children[48] (ages 8-13 years) and Adolescents[49] (ages 14-15 years) at T1 and T2. These self-perception scales have good validity valid in children without intellectual impairment[47-49].
- Self-perceived bike riding competence measured with the bike-riding item of the Pictorial Scale of Perceived Movement Skill Competence[50]. The scale from which this item is drawn has good reliability, and face and construct validity in children[50 51].
- Attendance and involvement for participants in the intervention group during the 3-day program as recorded by clinicians delivering the intervention group protocol. Any home-based bike skills training during the intervention period in both groups will be recorded by participants and parents each day of the intervention period and each week during the follow up period in a participant diary. Families will also be asked to assess the involvement of the child of a five point adjectival scale from minimally involved to very involved in the practice for each day of the seven-day intervention period.
- Quality of life measured by Child Health Utility-9D (CHU-9D)[52] at T1 and T2. The CHU-9D is a paediatric generic preference based measure of health related quality of life[52]. It consists of a descriptive system and a set of preference weights, giving utility values for each health state described by the descriptive system, allowing for calculation of quality-adjusted life-years for cost utility analysis. It consists of nine domains and has been validated in children aged 7-17 years. Data of resources and time used to deliver the task-specific approach to training bike skills and the parent-led home program will be collected by clinicians and parents and used for cost-effectiveness analysis.
- Fidelity assessed by examining the adherence of the clinicians and parents to the intervention and comparison group protocols. The amount of time practicing bike skills will be measured by participant diaries in both groups. Clinicians will also complete attendance logs for participants in the intensive program intervention group and will document adherence to the protocol as reported by the parent on the comparison group phone call. Specific fidelity to the intervention protocol will be by video analysis. One session of the intensive program per participant will be videoed and analysed for adherence to the protocol using the Motor Learning Strategies Rating Instrument - 20 Items[23].

Participating families will be asked to document any other therapy, health or medical interventions they receive during the study period on the participant diaries.

Exclusion during the study

All outcome data will be attempted to be collected for all enrolled participants with the exception of those who withdraw consent.

Treatment discontinuation

Participants in the intervention group or their parents may decide to stop the intervention at any time during the study. If a participant stops the intervention for any reason, all evaluations required for the immediate and final study visit will still be offered to the participant (unless the participant formally withdraws from the study).

Data analysis plan

Sample size calculation

Results of a survey conducted by the research team indicate that approximately 25% of children with CP (GMFCS I-II) had learnt to ride a two-wheel bike in the home environment led by their parents or caregivers[8], which is likely to be the key goal of many of the study participants. Within previous studies utilising the GAS to assess the effectiveness of similar interventions in children with CP, the proportion of goals attained or participants who have reached goal attainment has been reported between 66-86% [28 35 53-55].

Using the results of previous studies, this study is powered to find an absolute difference of 50% (from 25% in the home-program/comparison group to 75% in the intervention group) in the proportion of participants who reach goal attainment following the intervention. Assuming independent observations from individuals, a sample size of 19 in each group (38 in total) would be required to identify a difference in proportions of 50% with 80% power (based on a 2-sided test with a 5% level of significance). In this study, participants in the intervention group will receive the intervention in groups. It is likely that the outcomes for participants in the same group will be correlated or clustered hence the sample size has been inflated to account for this correlation. Assuming a small intra-cluster correlation of 0.1 between individuals within a cluster, and assuming an average cluster size of five, this equates to a design effect of 1.4, hence we will need to recruit 27 participants per arm (54 participants in total) to obtain the effective sample size of 38. Finally we inflate the required sample size to allow for 10% loss to follow-up, hence we plan to recruit a total of 60 participants (approximately 30 per group).

Statistical analysis

All statistical analysis will be conducted on an intention-to-treat basis where outcome data are available using STATA statistical software version 14[56]. Descriptive statistics will be used to characterise each group. Logistic regression will be used to assess the effect of providing the novel task-specific intervention compared to the parent-led home program on the primary outcome, bike-specific goal attainment, adjusted for site as used in the randomisation process. Logistic regression will also be used to

compare secondary binary outcomes between each group and linear regression will be used to compare secondary continuous outcomes between groups.

All analyses will be conducted using mixed effects models including a random effect to allow for the clustering of participants within therapy groups in the intervention arm. As a secondary analysis, all analyses will be repeated using a per-protocol analysis. In this analysis participants in the intervention group who discontinued the intervention prior to completing the three day program will be excluded from the analysis.

Participants will also be excluded from per-protocol analysis in either treatment group if any of the following protocol violations occur following randomisation and during the intervention and follow up periods

- Botulinum Toxin-A injections to the lower or upper limbs
- Musculoskeletal surgery or other major surgery that may affect their physical ability
- Insertion of an intrathecal baclofen pump
- Occupational therapy or physiotherapy related to training two-wheel bike skills other than the intervention or comparison group protocols

The economic appraisal will be conducted from a societal perspective. Cost-consequence analysis, including cost-effectiveness analysis and cost-utility analysis, will be carried out by comparing the incremental cost with the incremental benefit. The cost-effectiveness analysis will compare the costs to the primary and secondary outcomes demonstrating significance, and the cost-utility analysis will compare the costs to the outcomes as measured by the CHU-9D[52]. The costs associated with resources and time used for each group will be assessed and compared.

Handling of missing data

Prior to analysis, the amount of missing data will be explored, along with a comparison of distribution of key variables in individuals with and without missing data. If there is a reasonable amount of missing data and the data summaries suggest that the data are missing at random then all analyses will be presented following multiple imputation for missing data using baseline variables as auxiliary variables. Complete case analysis will also be conducted and reported. In the case there is little missing data, a complete case analysis will form the primary analysis.

ETHICS AND DISSEMINATION

This study was granted multisite approval by the Human Research and Ethics Committee at the Royal Children's Hospital (#36209). The trial is registered with the U.S. National Institutes of Health (NCT03003026) and recruitment is ongoing.

Data collected as part of this study will be entered and stored in electronic format on a REDCap secure, web-based database[57]. All other relevant electronic and paper data

files will be stored securely and accessible only to study investigators. Participant confidentiality and privacy will be strictly held in trust by all study personnel.

Given the low risk nature of trial, a data monitoring committee is not required. Adverse events (AEs) will be recorded from the time the participant signs the informed consent form until the end of the last study visit. Any serious adverse event occurring in a study participant will be reported to all involved ethics committees within 72 hours of occurrence.

This study is being completed as part of RT's Doctor of Philosophy (PhD – physiotherapy) at the University of Melbourne. It will form a major part of her thesis. The results of this study will submitted to peer-reviewed journals and presented to national and international conferences. Participating families will receive detailed summaries of the results of the study and a brief summary of the results will be distributed through the VCPR bi-annual newsletter and the CRE-CP e-newsletter/website.

SIGNIFICANCE

This study will contribute to the evidence base regarding the effectiveness of approaches to training bike skills in children with CP for attaining bike specific goals. Further, the range of secondary outcomes will allow for assessment of the effect of training bike skills on a range of meaningful outcomes for children and their families. The results of the economic evaluation will be used for policy and decision making.

INVESTIGATOR CONTRIBUTIONS

All named investigators contributed to the design of this trial protocol, to drafting and revising the manuscript and have approved this version for submission. Lead investigator Rachel Toovey is responsible for all aspects of study conduct with a particular focus on study oversight, recruitment, clinician training, reporting of adverse events, conducting study visits, outcome assessment, data management, and statistical methods. Dr Adrienne Harvey, A/Prof Jennifer McGinley and A/Prof Alicia Spittle are responsible for selected study procedures (including randomisation allocation) and study oversight. A/Prof Katherine Lee has contributed to statistical methods and will be involved in interpretation of the results. Dr Sophy Shih will contribute to economic appraisal. Rachel Toovey will lead the dissemination and translation of results, with contributions from all investigators.

ACKNOWLEDGEMENTS

We thank Frances Wright (parent advisor), Prof Andrew Davidson (Director, Melbourne Children's Trials Centre), A/Prof Adam Scheinberg, A/Prof Barry Rawicki (VPRS), Dr Sue Reid (Manager, VCPR) and Prof Dinah Reddihough (Murdoch Children's Research Institute) for their contributions to this protocol and in-kind support of this study.

REFERENCES

1. Stanley F, Blair E, Alberman E. How common are the cerebral palsies? Cerebral Palsies: Epidemiology and Causal Pathways. London: MacKeith Press 2000:22-29.
2. Bax M, Goldstein M, Rosenbaum P, et al. Proposed definition and classification of cerebral palsy. *Dev Med Child Neurol* 2005;47:571-76.
3. Bjornson K, Belza B, Kartin D, et al. Ambulatory physical activity performance in youth with cerebral palsy and youth who are typically developing. *Phys Ther* 2007;87:248-57.
4. Fernandes R, Sansecso A. Early physical activity promotes lower prevalence of chronic disease in adulthood. *Hypertens Res* 2010;33(9):926-31.
5. Novak I, McIntryre S, Morgan C, et al. A systematic review of interventions for children with cerebral palsy: state of the evidence. *Dev Med Child Neurol* 2013;55(10):885-910.
6. Australian Bureau of Statistics. Children's Participation in Cultural and Leisure Activities http://www.abs.gov.au/ausstats/abs@.nsf/Products/4901.0~Apr+2012~Main+Features~Recreational+activities?OpenDocument 2012 [accessed 18 February 2016 2016.
7. Palisano R, Rosenbaum P, Walter S, et al. Development and reliability of a system to classify gross motor function in children with cerebral palsy. *Dev Med Child Neurol* 1997;39:214-23.
8. Toovey R, Reid S, Harvey A, et al. Ability of ambulatory children with cerebral palsy to ride a bike and age at skill acquisition. *Dev Med Child Neurol* 2017;59(4):395-401.
9. Demuth SK, Knutson LM, Fowler EG. The PEDALS stationary cycling intervention and health-related quality of life in children with cerebral palsy: a randomized controlled trial. *Dev Med Child Neurol* 2012;54(7):654-61. doi: http://dx.doi.org/10.1111/j.1469-8749.2012.04321.x
10. Fowler EG, Knutson LM, Demuth SK, et al. Pediatric endurance and limb strengthening (PEDALS) for children with cerebral palsy using stationary cycling: a randomized controlled trial. *Phys Ther* 2010;90(3):367-81.
11. Siebert KL, DeMuth SK, Knutson LM, et al. Stationary cycling and children with cerebral palsy: case reports for two participants. *Phys Occup Ther Pediatr* 2010;30(2):125-38. doi: http://dx.doi.org/10.3109/01942630903578399
12. Sakzewski L, Ziviani J, Boyd R. Efficacy of Upper Limb Therapies for Unilateral Cerebral Palsy: A Meta-analysis. *Pediatrics* 2014;133(1):e175-204.
13. French B, Thomas LH, Leathley MJ, et al. Repetitive task training for improving functional ability after stroke. *Cochrane Database Syst Rev* 2007;17(4) doi: 10.1002/14651858.
14. Hubbard IJ, Neilson C, Carey LM. Task-specific training: evidence for and clinical practice. *Occup Ther Int* 2009;16(3-4):175-89.
15. Bar-Haim S, Harries N, Nammourah I, et al. Effectiveness of motor learning coaching in children with cerebral palsy: a randomized controlled trial. *Clin Rehabil* 2010;24(11):1009-20. doi: http://dx.doi.org/10.1177/0269215510371428

16. Thelen E, Smith L. Theoretical Models of Human Development (chapter 6). In: John Wiley and Sons, ed. Dynamic Systems Theories. London2007.
17. Shumway-Cook A, Woollacott M. Motor Control: Translating Research into Clinical Practice (Fourth Edition). Baltimore, MD: Lippincott Williams & Wilkins 2012.
18. Bleyenheuft Y, Arnould C, Brandao MB, et al. Hand and Arm Bimanual Intensive Therapy Including Lower Extremity (HABIT-ILE) in Children With Unilateral Spastic Cerebral Palsy: A Randomized Trial. *Neurorehabil Neural Repair* 2015;29(7):645-57.
19. Kumban W, Amatachaya S, Emasithi A, et al. Effects of task-specific training on functional ability in children with mild to moderate cerebral palsy. *Dev Neurorehabil* 2013;16(6):410-7.
20. Toovey R, Rawicki B, Harvey A. Outcomes of a goal directed intensive bicycle skills group program for children with cerebral palsy: a pilot case series. Australasian Academy of Cerebral Palsy and Developmental Medicine Conference. Adelaide, Australia: Dev Med Child Neurol, 2016:60-61.
21. Roberts G, Howard, K. Spittle A.J., Brown, N.C., Anderson, P.J., and Doyle, L.W. . Rates of early intervention services in very preterm children with developmental disabilities at age 2 years. *Journal of Paediatrics and Child Health* 2007 doi: doi:10.1111/j.1440-1754.2007.01251.x
22. Kiresuk T, Sherman R. Goal attainment scaling: a general method of evaluating comprehensive mental health programmes. *Community Ment Health J* 1968;4:443-53.
23. Ryan J, Levac D, Wright FV. Motor learning strategies rating instrument-20 items (MLSRI-20) instruction manual. Toronto, CA: Holland Bloorview Kids Rehabilitation Hospital, 2016.
24. Thorpe DE, Valvano J. The effects of knowledge of performance and cognitive strategies on motor skill learning in children with cerebral palsy. *Pediatr Phys Ther* 2002;14(1):2-15.
25. Thomas RE, Johnston LM, Sakzewski L, et al. Evaluation of group versus individual physiotherapy following lower limb intra-muscular Botulinum Toxin-Type A injections for ambulant children with cerebral palsy: A single-blind randomized comparison trial. *Res Dev Disabil* 2016;53-54:267-78.
26. Hemayattalab R, Arabameri E, Pourazar M, et al. Effects of self-controlled feedback on learning of a throwing task in children with spastic hemiplegic cerebral palsy. *Res Dev Disabil* 2013;34(9):2884-9.
27. Lowing K, Bexelius A, Brogren Carlberg E. Activity focused and goal directed therapy for children with cerebral palsy - do goals make a difference? *Disabil Rehabil* 2009;31(22):1808-16. doi: 10.1080/09638280902822278
28. Steenbeek D. Goal attainment scaling in paediatric rehabilitation. Utrecht University, 2010.
29. Lowing K, Bexelius A, Brogren Carlberg E. Activity focused and goal directed therapy for children with cerebral palsy--do goals make a difference? *Disabil Rehabil* 2009;31(22):1808-16. doi: http://dx.doi.org/10.1080/09638280902822278

30. Lowing K, Bexelius A, Brogren-Carlberg E. Goal-directed functional therapy: a longitudinal study on gross motor function in children with cerebral palsy. *Disabil Rehabil* 2010;32(11):908-16.

31. Kuhlthau K, et al. Evidence for family-centered care for children with special health care needs: a systematic review. *Acad Pediatr* 2011;11:136-43.

32. Novak I, Cusick A, Lannin N. Occupational therapy home programs for cerebral palsy: double-blind, randomized, controlled trial. *Pediatrics* 2009;124(4):e606-14. doi: http://dx.doi.org/10.1542/peds.2009-0288

33. Palisano R. Validity of goal attainment scaling in infants with motor delays. *Phys Ther* 1993;73(10):651-58.

34. Steenbeek D, Ketelaar M, Lindeman E, et al. Interrater reliability of goal attainment scaling in rehabilitation of children with cerebral palsy. *Archives of Physical Medicine & Rehabilitation* 2010;91(3):429-35.

35. Steenbeek D, Ketelaar M, Galama K, et al. Goal attainment scaling in paediatric rehabilitation: a critical review of the literature. *Dev Med Child Neurol* 2007;49(7):550-56.

36. Toovey R, Harvey AR, McGinley JL, et al. Bike Skills Training for Children With Cerebral Palsy. US National Library of Medicine Clinical Trials Register ID: NCT03003026. ClinicalTrials.gov 2016.

37. Krasny-Pacini A, Evans J, Sohlberg M, et al. Proposed criteria for appriasing goal attainment scales used as outcome measures in rehabiliation research. *Arch Phys Med Rehabil* 2016;97:157-70.

38. Wassenberg-Severijnen J, Maas C, Custers J, et al. Standardization of the Dutch 'Pediatric Evaluation of Disability Inventory' (PEDI). Chapter 5, Pediatric Evaluation of Disability Inventory (PEDI): Calibrating the Dutch Version. Utrect University, 2005.

39. Halayko J. You Can Ride Too! An Exploration of the Guided Discovery of Two-wheeled Cycling Skills by Youth with Intellectual Disabilities. University of Alberta, 2014.

40. Custers J, et al. Discriminative validity of the Dutch PEDI. *Arch Phys Med Rehabil* 2002;83:1437-41.

41. Halayko J, Magill-Evans J, Smith V, et al. Enabling 2-wheeled cycling for youth with Down Syndrome. *Pediatr Phys Ther* 2016;28:224-30.

42. Haley SM, Coster WJ, Dumas HM, et al. Pediatric Evaluation of Disability Inventory Computer Adapative Test - Development, Standardization and Administration Manual http://www.pedicat.com.2012 [accessed July 2016.

43. Activ8 (TM) physical activity monitor https://www.activ8all.com/2015 [accessed 17 July 2016.

44. Crocker PRE, Bailey DA, Faulkner RA, et al. Measuring general levels of physical activity: preliminary evidence for the Physical Activity Questionnaire for Older Children. *Med Sci Sports Exerc* 1997;29(10):1344-9.

45. Gorter J, et al. Accelerometry: A feasible method to quantify physical activity in ambulatory and nonambulatory adolescents with cerebral palsy. *Int J of Ped* 2012

46. Janz KF, Lutuchy EM, Wenthe P, et al. Measuring Activity in Children and Adolescents Using Self-Report: PAQ-C and PAQ-A. *Medicine & Science in Sports & Exercise* 2008;40(4):767-72.

47. Harter S, Pike R. The Pictoral Scale of Percevied Competence and Social Acceptance for Young Children: Manual https://portfolio.du.edu/SusanHarter/page/44342: University of Denver; 1983 [accessed July 2016.
48. Harter S. Self-Perception Profile for Children https://portfolio.du.edu/SusanHarter/page/44210: Unviersity of Denver; 2012 [accessed July 2016.
49. Harter S. Self-Perception Profile for Adolescents https://portfolio.du.edu/SusanHarter/page/44210: University of Denver; 2012 [accessed July 2016.
50. Barnett LM, Ridgers ND, Zask A, et al. Face validity and reliability of a pictorial instrument for assessing fundamental movement skill perceived competence in young children. . *J Sci Med Sport* 2015;18:98-102.
51. Barnett LM, Vazou, S., Abbott, G., Bowe, S.J., Robinson L.E., Ridgers N.D., Salmon, J. . Construct validity of the pictorial scale of Perceived Movement Skill Competence. *Psychol Sport Exerc* 2016;22:294-302.
52. Stevens KJ. Assessing the performance of a new generic measure of health related quality of life for children and refining it for use in health state valuation. *Appl Health Econ Health Policy* 2011;9(3):157-69.
53. Ahl LE, Johansson E, Granat T, et al. Functional therapy for children with cerebral palsy: an ecological approach. *Dev Med Child Neurol* 2005;47:613-19.
54. Lowing K, Bexelius A, Brogren Carlberg E. Activity focused and goal directed therapy for children with cerebral palsy-do goals make a difference? *Disabil Rehabil* 2009;31(22):1808-16.
55. Sorsdahl AB, Moe-Nilssen R, Kaale HK, et al. Change in basic motor abilities, quality of movement and everyday activities following intensive, goal-directed, activity-focused physiotherapy in a group setting for children with cerebral palsy. *BMC Pediatr* 2010;10:26.
56. StataCorp. Stata Statistical Software: Release 14.: College Station, TX, 2015.
57. Harris P, Taylor R, Thielke R, et al. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42(2):377-81.

Figure 1 Study timeline, t_{-1}: enrolment and baseline assessment time point, t_0 randomisation and allocation time point, t_1: first follow up assessment time point, t_2: final follow up assessment time point, MCH: Monash Children's Hospital, PICF: Participant information and consent form, RCH: The Royal Children's Hospital, VCPR: Victorian Cerebral Palsy Register, VPRS: Victorian Paediatric Rehabilitation Service.

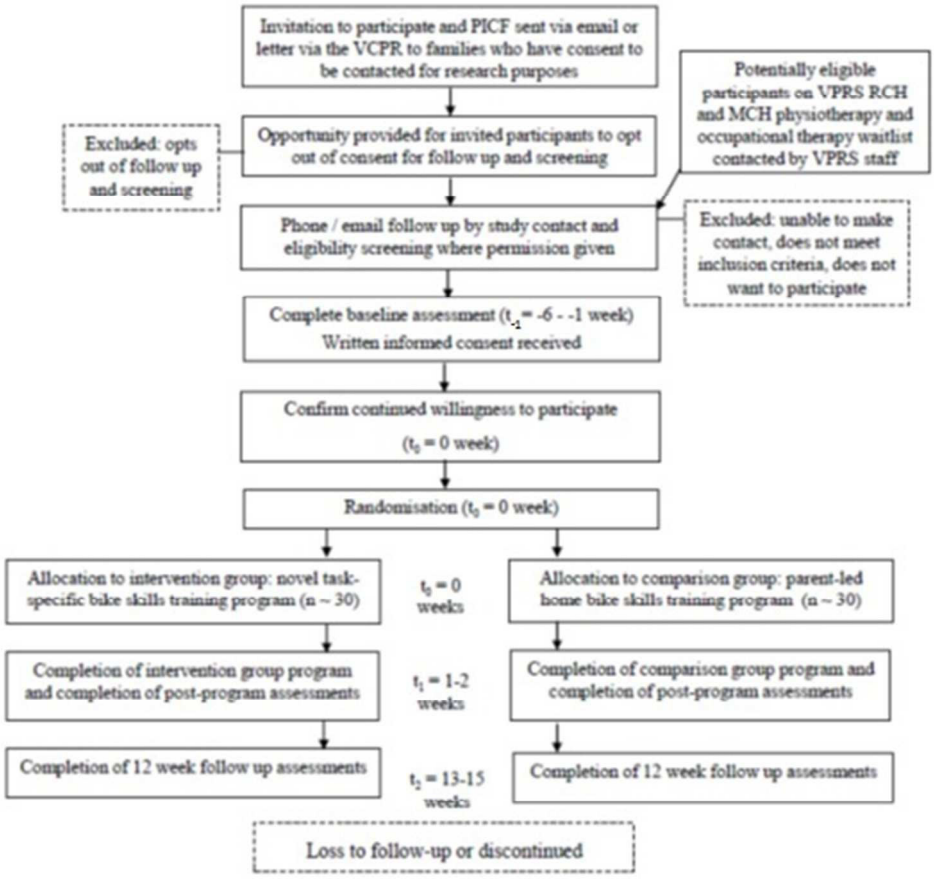

Figure 1 Study timeline, t-1: enrolment and baseline assessment time point, t0 randomisation and allocation time point, t1: first follow up assessment time point, t2: final follow up assessment time point, MCH: Monash Children's Hospital, PICF: Participant information and consent form, RCH: The Royal Children's Hospital, VCPR: Victorian Cerebral Palsy Register, VPRS: Victorian Paediatric Rehabilitation Service.

49x44mm (300 x 300 DPI)

Appendix 1: Schedule of assessments

VARIABLES		STUDY PERIOD			
	Initial Eligibility Screen	Baseline Assessment	Allocation	Follow up study visits	
TIME POINT**	*t_{-1}*	t_{-1} = -6 to -1 weeks	t_0 = 0	*t_1 = 1-2 weeks*	*t_2 = 13-15 weeks*
Confirmed CP	X				
GMFCS	X	X (Confirm)			
Age	X				
Intellectual ability	X				
Healthy care giver available	X				
Live in Victoria / near border	X				
Appropriate bike and helmet	X				
Medical clearance	X				
BonT-A injections or surgery (including insertion of baclofen pump) in last 6 months	X	X		X	X
No other bike related therapy during intervention and follow up period				X	X
Informed Consent		X			
Allocation			X		
Topography and motor type		X			
Manual Ability Classification Scale (MACS)		X			
Previous bike riding practice		X			
Parent rated importance of bike skills goal attainment		X			
Parent bike skills competence and interest		X			
Parent social risk questionnaire		X			
Goal attainment (GAS)		X		X	X
Two-wheel bike skills (PEDI-NL & Cycling skills checklist)		X		X	X
Functional skills (PEDI-CAT)		X		X	X

Physical activity behaviour (accelerometer & PAQ-C)		X			X
Self-perception (SPP-C/A)		X		X	X
Self-perceived bike riding competence		X		X	X
Cost Utility (CHU -9D)		X		X	X
Attendance and involvement in intervention group				X	X
Practice in intervention and comparison group				X	X
Child involvement in intervention and comparison group training				X	X
Other therapy or medical interventions				X	X
Adverse events		X		X	X

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Abstract p1, protocol p1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Abstract p1, protocol p14, 18
	2b	All items from the World Health Organization Trial Registration Data Set	Abstract p1
Protocol version	3	Date and version identifier	Protocol p1
Funding	4	Sources and types of financial, material, and other support	Protocol p1
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Abstract p1, protocol p1
	5b	Name and contact information for the trial sponsor	N/A
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A

	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	Protocol p15
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	Abstract p2, protocol p4
	6b	Explanation for choice of comparators	Protocol p2, 9-10
Objectives	7	Specific objectives or hypotheses	Protocol p5
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	Abstract p2, Protocol p5
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	Protocol p5
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	Protocol p6
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Protocol p8-10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	Protocol p14
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Protocol p12, 15
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Protocol p14

Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	Protocol p10-12
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1, Appendix 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	Protocol p13
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	Protocol p6-7
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	Protocol p8
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	Protocol p8
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	Protocol p8
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	Protocol p8
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	Protocol p8
Methods: Data collection, management, and analysis			

Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	Protocol p10-12
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	Protocol p12-13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	Protocol p14
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	Protocol p13-14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Protocol p13-14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	Protocol 13-14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	Protocol p14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	Protocol p14
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Protocol p14-15
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Protocol p1, 14
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	Protocol p14-15
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Protocol p7
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	Protocol p14
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Protocol p1
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	Abstract p2
	31b	Authorship eligibility guidelines and any intended use of professional writers	N/A
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not attached

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.