BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057668
Article Type:	Protocol
Date Submitted by the Author:	23-Sep-2021
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Keywords:	Developmental neurology & neurodisability < PAEDIATRICS, SPORTS MEDICINE, REHABILITATION MEDICINE

TITLE

Study protocol for Running for health (Run4Health CP): a multi-centre, assessor-blinded randomized controlled trial of 12 weeks of twice weekly Frame Running training versus usual care to improve cardiovascular health risk factors in children and youth with cerebral palsy

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Word count

5934/4000

ABSTRACT

Introduction

Children and youth with moderate-severe (Gross Motor Function Classification System [GMFCS] levels III-V) cerebral palsy (CP) participate less frequently in physical activities compared to peers without CP. They also experience elevated risk of cardiorespiratory morbidity and mortality in adulthood. Frame Running (RaceRunning) is a new athletics discipline using a supportive running frame, and is an accessible option for physical activity participation for people with moderate-severe CP. There is no high-quality evidence for the effect of Frame Running on cardiovascular disease in children and young people with CP. The primary aim of this study is to conduct a randomized controlled trial of the effect of 12 weeks of Frame Running training on risk factors for cardiovascular disease.

Methods and Analysis

Fifty-two children and youth with CP (age 8-20 years) classified in GMFCS levels II-V will be recruited across three sites and randomized to receive either 12 weeks of Frame Running training twice weekly for 60 minutes, or 12 weeks of usual care. Outcomes will be measured at baseline, immediately post-intervention, and 12 weeks later for retention of training effects. Outcomes include cardiorespiratory fitness, blood pressure, objectively measured habitual physical activity, body mass index, waist circumference, percentage body fat, gross motor function capacity, community participation, feasibility, tolerability, and safety. Adverse events will be monitored, and participants and/or their caregivers will be interviewed in focus groups to discern their experiences, including barriers and facilitators to ongoing, sustainable participation in Frame Running.

Ethics and Dissemination

The Children's Health Queensland Hospital and Health Service and the University of Queensland Human Research Ethics Committees have approved this study. Results will be disseminated academically in peer-reviewed journals and scientific conferences; to therapists and coaches through professional and athletic organisations; and to people with CP and their families.

Registration

Australian New Zealand Clinical Trials Registry number: ACTRN12621000317897p

ARTICLE SUMMARY

Strengths and limitations of this study

- This randomized controlled trial of Frame Running training in children and youth with cerebral palsy is powered to detect change on the primary outcome measure of cardiovascular fitness.
- Retention (sustainability) of changes will be examined at a follow-up 12 weeks after the training sessions are complete.
- Children and youth with severe functional mobility limitations and intellectual disability will be included.
- A validated maximal exercise test will not be conducted.

INTRODUCTION

One in 700 Australians have cerebral palsy (CP), a permanent but not unchanging disorder of posture and movement caused by a disturbance to the developing foetal or infant brain.[1] Children with CP participate in physical activities less often compared to peers without CP.[2] Children with CP also have high levels of sedentary behaviour,[3] apparent from early infancy and peaking by four to five years of age when followed through to middle childhood.[4] Adults with CP experience increased risk of non-communicable diseases associated with low PA including cardiovascular disease, mental illness, osteoporosis and osteoarthritis (Odds ratios 1.3-5.8).[5] There is evidence that the disparity in non-communicable disease risk begins early, with a large population-based cohort study demonstrating increased risk of mental health disorders in children (6-17 years of age) with CP compared to children without CP.[6] In this study, pain and low physical activity level explained part of the relationship between CP and depression.[6]

Life expectancy in people with CP in general is only slightly reduced compared to the people without CP, however those individuals with moderate-severe motor impairments have significantly lower life expectancy.[7] The causes of early death in people with CP are most frequently respiratory and cardiovascular diseases,[8] with respiratory illness the leading cause of death in children with CP.[9] An Australian prospective population-based register study following n=3507 individuals with CP determined that inability to walk independently (an indicator of severe CP), was the strongest predictor of mortality in people with CP (adjusted hazard ratio 6.2).[10] There is expert consensus that increasing aerobic fitness and PA in children with severe CP is likely to ameliorate the severity of acute respiratory illness.[9] Despite this, recent systematic reviews have demonstrated that there are no effective physical activity interventions for people with CP that do not walk independently, and interventions for children who can walk independently may not have a clinically meaningful effect on

physical activity behaviours including habitual physical activity and participation in physical activities.[11 12] Contributing factors to inefficacy may have included: selection bias (inclusion of children with the highest level of physical activity and physical functioning), failure to address environmental, contextual and behavioural barriers to physical activity, issues with outcome measurement,[11] and dosing below minimum recommended guidelines.[13] It is clear that there is an urgent need for high quality research into physical activity interventions of sufficient dose and duration in youth with CP who have major limitations in walking ability. Furthermore, such interventions need to be safe, community-based, informed by consumer needs, and aimed to enable ongoing, normal community participation and inclusion.

Frame Running, formerly known as RaceRunning, is a para-athletics discipline recently sanctioned by World Para Athletics (the International Paralympic Sports Federation for athletics). Frame Running was invented in 1991 by Connie Hansen, an Occupational Therapist and para-athlete and Mansoor Siddiqi, a para-athlete with CP competing in the now defunct discipline of backward wheelchair racing (foot-propelled). Frame Running utilises a three-wheeled frame with low rolling resistance for support, enabling running in people with otherwise severe mobility limitations (see Figure 1). In the absence of an existing systematic review of the literature, an author search conducted on 21 September 2021 for articles indexed in the PubMed database, using the terms “RaceRunning” OR “Frame Running” OR “race running” AND “cerebral palsy” located in title/abstract (with additional hand search of reference lists for included articles) returned only seven studies: one pilot single-group pre-post trial,[14] one study protocol for a pilot randomized feasibility study,[15] one reliability study for a Frame Running-specific field exercise test,[16] two cross-sectional studies examining relationship between impairments and Frame Running performance,[17 18] and two cross-sectional studies on kinesiologic and metabolic responses or adaptations to use of running frames.[19 20] The pre-post pilot trial included n=15 adolescents and young adults with CP (age

range 9-29 years, Gross Motor Function Classification System [GMFCS] levels I-IV) and demonstrated that 12 weeks of twice weekly Frame Running training led to on average, a 34% increase in cardiorespiratory endurance and a 9% increase in thickness of the medial gastrocnemius muscle.[14] Frame Running can evoke a heart rate commensurate with high intensity exercise,[19] and uses large muscle groups in a reciprocal way that may have functional cross over to enhanced mobility.[20] A larger (n=25) pre-post pilot study of once weekly Frame Running training for 24 weeks duration is planned.[15] This study with no accompanying sample size calculation has the potential to be underpowered and/or underdosed to detect improvements in cardiometabolic risk factors. Furthermore, as the study is unrandomized, the quality and certainty of the evidence provided will necessarily be lower than a randomized study.

We therefore aim to conduct an adequately powered randomized controlled trial of Frame Running training in children and youth with CP on cardiometabolic risk factors and related outcomes (Run4Health CP). This study may therefore provide evidence that cardiometabolic risk factors can be modified in children and youth with CP who have moderate to severe motor impairment and high support needs in mobility. This evidence may have critical patient and clinical impacts through support of funding for running frames and may help to foster development of the discipline and expand participation opportunities.

[Insert Figure 1 about here]

METHODS AND ANALYSIS

Objectives

The primary objective of this study is to compare the effect of 12 weeks of Frame Running training versus usual care control on cardiovascular fitness (endurance) on the Six Minute

RaceRunner Test (6MRRT) and 1-minute heart rate recovery (HRR_{1min}) following exercise testing immediately at post-intervention and at 12 weeks post-intervention.

Secondary objectives are to compare the effect of 12 weeks of Frame Running training versus usual care control immediately post-intervention and at 12 weeks post-intervention on:

1. other cardiovascular risk factors including: resting blood pressure, habitual physical activity level, body mass index, percent body fat, and waist circumference.
2. gross motor activity capacity including gross motor function and Frame Running-specific activity limitation tests
3. community participation.

The tertiary objective of this study is to determine whether 12 weeks of Frame Running training is feasible, tolerable, safe, and sustainable in the study population, including whether participants report that it induces additional pain and fatigue when compared to usual care.

Trial Design

Run4Health CP is a pragmatic, single (assessor)-blind randomized controlled, multi-centre trial with two parallel groups. The primary timepoint is immediately post-intervention (12 weeks post-baseline) and the secondary timepoint is 12 weeks post-intervention (24 weeks post-baseline). The study will be conducted in three Australian cities, Brisbane (n=24), Cairns (n=18) and Sydney (n=10). Assessment of outcome measures and Frame Running training will be conducted at community synthetic athletics tracks and nearby associated indoor sports facilities at a time convenient to participants and their caregivers. Randomization will be stratified according to GMFCS (II-III/IV-V) and site (Brisbane vs Cairns vs Sydney), with 1:1 assignment to Frame Running training or usual care control.

Recruitment commenced on 16 August 2021 with the first participant enrolment expected in October 2021.

Eligibility Criteria

Participants eligible for the trial must comply with all of the following eligibility criteria at randomization: (1) diagnosis of cerebral palsy and classified in GMFCS levels II-V, (2) between 8.00 to 20.99 years of age, (3) live within 150km of one of the trial sites, (4) have not engaged in formal Frame Running training within the last 6 months in the opinion of the Principal Investigator, (5) can understand and follow the directions of the coach and assessors for the purposes of training safely and completing outcome measurement in the opinion of the Principal Investigator.

Participants are excluded if at any time: (1) the child/youth has orthopaedic and/or neurological surgery within 6 months prior to baseline or during the study period requiring a period of recovery that would exclude the participant from training for more than one week, (2) the child/youth has uncontrolled epilepsy, medical fragility, and/or serious precautions not able to be accommodated (e.g. significant history of atraumatic lower limb fractures or sacral pressure injuries etc.) precluding participation in moderate-vigorous intensity Frame Running, (3) caregiver English language skills are not sufficient to understand the study information, provide informed consent and/or complete study questionnaires.

Interventions

Frame Running Training Group

Frame Running training will consist of two, 60-minute sessions per week for 12 consecutive weeks (total dose 24 hours). Established guidelines for aerobic exercise to improve cardiovascular health in typically developing individuals recommend a minimum frequency

of three sessions per week.[13] There is evidence however that two sessions per week is adequate in deconditioned individuals with CP to improve aerobic fitness,[13] and this was demonstrated in the pilot pre-post study of Frame Running training by Hjalmarsson et al (2020).[14] This can likely be attributed to the dose-response relationship between PA and cardiorespiratory outcomes, whereby even small increases in PA in previously inactive individuals can result in clinically meaningful improvements in health.[21] Provision of only two sessions per week may also increase the likelihood that participants can comply with the intervention (considering issues such as time and financial constraints relative to a third session).

Participants will attend Frame Running training in groups of approximately three, matched by age and/or ability if possible. Sessions will be administered by a coach with qualifications in Physiotherapy and/or Exercise Physiology. Participants in the training group are permitted to receive their usual care from non-study providers (as per concomitant care) with no restriction.

Frame Running training sessions will consist of a combination of (1) anaerobic Frame Running (i.e. starts and sprints drills using established athletic training principles), (2), aerobic Frame Running (i.e. steady running working towards ≥15 minutes duration), and (3) task-specific functional training for Frame Running technique and skills (e.g. braking, steering, propulsion strategies, running form, and power). Training sessions will increase in difficulty in a stepwise fashion, with the aim to initially develop basic skills in operating a running frame, working towards maintaining moderate-vigorous exercise intensity throughout a 60-minute session. A training load of 60-75% of peak heart rate can elicit a 9-40% increase in peak aerobic capacity with 2-4 sessions per week for minimum 20 mins in individuals with CP.[13] Based on a literature review of exercise training studies, proposed ideal exercise parameters for individuals with CP are: an intensity between 60–95% of peak

heart rate, between 40–80% of the heart rate reserve (HRR), or between 50–65% of VO_{2peak}.[13] To monitor adherence to this exercise intensity, participants will wear a Polar Verity Sense (Polar Electro Oy, Kempele Finland) optical heart rate monitor on the non-dominant upper limb during training sessions with output observed by the coach and/or assistants (e.g. undergraduate physiotherapy or exercise physiology students). As suggested by Verschuren et al., peak heart rate will be estimated at 194 beats per minute for children and youth with CP in the absence of maximal exercise testing.[22] Therefore, the target heart rate will be between 116-185 beats per minute.

Running frames are registered in the low-risk Medical Device Class 1 category on the Australian Register of Therapeutic Goods. They are manufactured overseas and are imported to Australia by Dejay Medical and Scientific Pty Ltd. There are currently two brands available in Australia, "RAD - Trike - Disability vehicle, cycle, tricycle, foot-propelled" (ARTG: 345236), and "By Connie Hansen - Disability vehicle, cycle, tricycle, foot-propelled" (ARTG: 309224). Both types of running frames may be used in the trial according to availability and suitability, as the differences between these brands are expected to be superficial considering the context of the trial (novice and beginner Frame Running athletes, recreational style participation with elementary competition). Where possible, the same frame will be used by each participant throughout the study period with consistent attachments, seat height, and chest plate angle/depth unless these are adapted for performance reasons.

Usual Care Control Group

Participants in the control group will receive their usual care from non-study providers (type/dose/content as per concomitant care). This will determine the effect of Frame Running training in addition to usual care, which already contains active treatments such a

physiotherapy and/or occupational therapy. Participants in the control group will not be offered Frame Running training and will be asked to refrain from participating in Frame Running until they have exited the study, however, this will not be actively prevented for ethical reasons. As Frame Running requires access to a running frame, and participants are not expected to have their own frame, it is expected that few participants in the control group will participate in Frame Running during the study period.

Following outcome measurement at the final time point, participants in the control group will be provided with an information package regarding local Frame Running training sessions, running frame fitting results (e.g. frame size required and attachments), and advice about how to obtain a running frame and participate in the sport. They will also receive up to two phone calls from a therapist providing physical activity counselling and advice. The aim of this package of supports is to improve equity in access to Frame Running opportunities for those otherwise receiving a no-treatment control.

Modifications and Adaptations

Heart rate data will be used to adjust the session in real time and to tailor the progression of session difficulty from week to week. Individual tailoring will also accommodate variability in participants' propulsion strategies, motor type/distribution, activity limitations, age, and interests. If any unexpected, unusual, or additional pain or fatigue beyond what is considered "normal" is experienced by a participant allocated to the Frame Running training group, this will be discussed with the participant and their caregiver and modifications to the training program may be implemented. Unexpected or unusual pain or fatigue in the training group will be recorded as an adverse event. Other participant characteristics may necessitate modification or adaptation to the training program, including but not limited to intellectual

disability, injury, hearing and/or vision impairment, tactile and/or proprioceptive impairment, behavioural and/or emotional dysregulation. Modifications may include reduction in dose, changes to training session content, use of assistive technology (hearing aids, visual aids etc.), visual guides, caregiver involvement, and/or advice and education regarding management of pain, injury and fatigue.

Adherence and Fidelity

The training content has been manualized to facilitate consistent application by coaches across trial sites and participants, and to promote adherence to the prescribed dose. Several strategies will be applied to optimize the participant's frequency of attendance at sessions and level of involvement (which is defined as the subjective experience of participation while attending, and includes elements such as engagement, motivation, persistence, and affect[23]). These strategies are hypothesized to fulfil participants' basic psychological needs of autonomy, competence and relatedness according to Self-Determination Theory,[24] which has been demonstrated to underpin physical activity interventions in children with CP[25]:

1. Training activities will be individually tailored as described above. This is likely to facilitate a "just right challenge" and fulfil participants' need for competence.[25]
2. Training will occur in groups of approximately three, matched where possible for age and/or ability. Training together with peers, with social group dynamics managed carefully, is likely to promote social connection and fulfil participants' need for relatedness.[26]

3. Coaches will use autonomy-supportive, empathetic communication with participants and families. Coaches will facilitate participant self-efficacy through teaching positive self-talk about performance and will promote positive peer to peer encouragement.[25]

Furthermore, training sessions will take place in locations where Frame Running squads train on a regular basis. This provides an ongoing avenue for normal, regular participation in the sport once the free clinical trial sessions conclude.

Individual adherence to the training manual will be recorded on a session-by-session basis by coaches. Measures include:

1. Percentage of sessions attended (including partial attendance).
2. Percentage of training drills completed according to the manualized content.
3. Percentage of session duration spent within the target heart rate threshold for training intensity.
4. List of modifications or adaptations.

Reasons for missed or incomplete sessions will be recorded. Adherence data will be reported alongside study outcomes.

Concomitant Care

Participants in both groups may continue any usual care from non-study providers throughout the study period (except Frame Running in the usual care control group). Type, dose and duration of usual care is likely to vary widely between participants owing to individual needs, access, and funding arrangements. This could include Botulinum Toxin-A injections, serial casting, and a broad array of exercise and movement-based therapies. Participants in both groups will be asked to record frequency of participation in Frame Running and other

physical activities, and frequency/type/dose of usual care therapies from non-study providers from allocation to exit using a Usual Care Diary.

Outcomes

Primary Outcome

Cardiovascular health (primary)

Distance (metres) covered in the Six Minute RaceRunner Test (6MRRT).[16] The 6MRRT is a validated measure of RaceRunning endurance with good test-retest reliability (ICC=0.78-0.91) in children classified in GMFCS levels III and IV. The 6MRRT is theoretically a submaximal exercise test, however it is likely that many participants will achieve almost maximal heart rate.

Secondary Outcomes

Cardiovascular health (secondary)

Heart Rate Recovery in 1 minute (HRR_{1min}) will be taken immediately following the 6MRRT. HRR_{1min} is strongly associated with cardiac mortality and is responsive to a 12-week cardiac rehabilitation program in children following heart surgery.[27] Children and youth will wear a Polar Verity Sense Optical HR monitor on the less-impaired upper arm during testing.

Resting blood pressure will be measured using an automated arm-cuff sphygmomanometer (valid and reliable).[28] Resting systolic and diastolic Blood Pressure (BP) in mmHg is a traditional risk factor for cardiometabolic disease in individuals with CP,[28] and systolic BP is associated with cardiorespiratory fitness, central adiposity and BMI in children with CP.[29]

Systolic and diastolic BP were responsive to a 12-week training program in youth with Down Syndrome.[30]

Habitual physical activity will be quantified using accelerometry, a valid, reliable and feasible method in youth with moderate to severe CP.[31] Participants will wear an ActiGraph GT3X+ on the less-impaired wrist and less-impaired anterior thigh for 7 days during waking hours during their usual activities (free-living). Data will be processed to identify time spent in different postures and activities using machine learning algorithms; a combined thigh and wrist classification model has been validated in children classified in GMFCS levels III and IV.[31]

Body mass index (BMI, kg/m^2) will calculated according to the equation: BMI = weight (Kg)/height^2 (m). Weight will be taken using the same calibrated digital scale at each site and height taken using the same stadiometer at each site for all participants. Participants that are unable to stand unassisted will access chair scales. If body shape distortion is severe and/or standing height is not feasible, then height will be measured using a recumbent measuring board if available or will be estimated using segmental limb length (knee height).[32] Anthropometric measures will be converted to Z-scores using age and gender specific reference data for the general population.[33]

Waist circumference (cm) will be measured to the nearest millimetre at the midline level using a non-stretchable tape measure.[34]

Percentage body fat will be estimated based on the triceps and subscapular skinfold thickness using CP-specific equations.[35] This will be measured using calipers (Harpenden Skinfold Caliper, Baty International, West Sussex UK) by trained investigators.

Gross motor capacity

Gross motor function will be assessed using GMFM-66, a criterion referenced observation measure developed using Rasch modelling to measure gross motor function of children with CP.[36] The GMFM-66 has established construct validity, high test-retest reliability (ICC 0.99) and is responsive to change.[36 37]

Frame Running-specific activity limitation will be assessed using 100 metre sprint (time in seconds), distance covered in four strides (metres, average of two valid trials), and step count in 20 metres (steps, average of two valid trials). The assessment of function is activity specific and therefore outcomes should be strongly related to the activity of interest.[38] These assessments are investigator-developed and will be subject to further independent assessment of their validity and reliability.

Participation

Community participation will be evaluated using the Participation and Environment Measure for Children and Youth (PEM-CY).[39] The PEM-CY is a caregiver-report questionnaire with good test-retest reliability and internal consistency.[39] Youth 18 years and older will be invited to self-report the questionnaire. Summary scores for participation frequency, involvement, and percent environmental supportiveness will be calculated.

Feasibility, tolerability and safety

Feasibility, tolerability and safety will be measured on a weekly basis in both groups using the Wong-Baker FACES® rating scale (pain),[40] Fatigue Severity Scale (FSS, fatigue),[41] and for the training group only, training load (Rate of Perceived Exertion [RPE] on the OMNI

RPE[42] multiplied by session duration).[43] Monitoring of adverse and unintended events including injuries will be undertaken throughout the study.

Classification systems and demographic characteristics

The following validated classification systems will be applied: Gross Motor Function Classification System Expanded and Revised (GMFCS),[44] Manual Abilities Classification System (MACS),[45] Communication Function Classification System (CFCS),[46] Visual Function Classification System (VFCS),[47] Eating and Drinking Ability Classification System (EDACS).[48] The VFCS and EDACS will be applied owing to the contribution of the visual system to athletic performance,[49] and the association between eating and drinking ability and nutrition status, which is relevant to body composition, muscle mass, functional ability and performance in training programs in people with CP.[50 51] If known, the participant's Frame Running Sport Class under the two existing classification systems will be recorded (RR1/RR2/RR3 and/or T71/T72). If unknown (or not yet classified), a provisional classification will be performed following the process outlined by Athletics Australia.

The following participant demographic characteristics will be collected to characterize the sample: participant age, sex, dominant hand, socioeconomic status, presence of comorbid diagnoses, list of up to nine sports/PAs the participant attended in the last 12 months, and caregiver frequency of participation in structured and unstructured sports/PAs in the last four months. Participants will also be screened for medical conditions that may be precautions to high intensity exercise using a running frame requiring attention or adaptation but not meeting exclusion criteria (e.g. known stable cardiovascular or respiratory condition etc.).

Participant Timeline

Run4Health CP schedule of assessments and interventions are provided below in Table 1 and the CONSORT[52] study flow diagram is provided in Figure 2.

Table 1: Schedule of assessments for Run4Health CP study.

TIMEPOINT	Enrolment	Allocation/ Baseline	Intervention	Immediately post-intervention (12 weeks)	Retention (24 weeks)
VISIT NUMBER:	Screen	T1		T2	T3
Participant contact	X				
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
Frame running training			X		
Usual care control			X		
ASSESSMENTS:					
Classification systems (GMFCS, MACS, CFCS, VFCS, EDACS)		X			
Demographic questionnaire		X			
Frame Running provisional sport class		X			
Six minute RaceRunner test (6MRRT)		X		X	X
Heart rate recovery in 1 minute (HRR_{1min})		X		X	X
Resting blood pressure		X		X	X

7-day free-living accelerometry for habitual physical activity (ActiGraphGT3X+ thigh and wrist)		X		X	X
Body Mass Index (BMI)		X		X	X
Percent body fat		X		X	X
Waist circumference		X		X	X
Gross Motor Function Measure 66 (GMFM-66)		X		X	X
Frame Running activity limitation tests		X		X	X
Participation and Environment Measure for Children and Youth (PEM-CY)		X		X	X
Wong-Baker FACES rating		X	X	X	X
Fatigue severity scale (FSS)		X	X	X	X
Monitoring of adverse and unintended events		X	X	X	X
Usual care diary		X	X	X	X

[Insert Figure 2 about here]

Sample Size

Based on the primary outcome of 6MRRT which has a smallest detectable difference of approximately 150m and sample SD of 150m,[16] a sample size of n=44 will detect at least this difference at 90% power and two sided 5% significance level. To allow for up to 15% attrition, n=52 (n=26 per group) will be recruited.

Recruitment

Strategies to achieve adequate participant enrolment to reach the target sample size are as follows:

1. Clinical database: potential participants will be identified on a clinical database held and maintained by the Queensland Paediatric Rehabilitation Service (QPRS) at the Queensland Children's Hospital and the Sydney Children's Hospitals Network (SCHN). Caregivers of children/youth who have previously consented to receive communications about research studies will be sent a copy of the study flyer to their contact email or postal address.
2. Clinical service: Children and youth with cerebral palsy attending an associated clinical service within QPRS and SCHN will be identified by their treating clinicians based on eligibility criteria. Clinicians will ask permission to discuss the project and gain consent from the family to be contacted by a project staff member.
3. Patient advertising: Patient waiting areas at associated clinical services within QPRS and SCHN will display the approved flyer during the recruitment period.
4. Newsletter: The flyer will be included in the newsletters distributed by associated clinical services within QPRS and SCHN and research groups of the investigators.
5. Websites: The flyer will be posted on the research websites of the investigators.
6. Social media/word of mouth: The flyer will be posted on social media websites which may include but are not limited to Facebook, Twitter, and Instagram. The electronic version of the flyer may then be shared by third parties.

Allocation and Blinding (Masking)

Participants will be randomly assigned to either Frame Running training or usual care control with a 1:1 allocation as per a computer-generated randomization schedule using the Research Electronic Data Capture (REDCap®) randomization module, stratified by GMFCS (II-III/IV-V) and site (Brisbane vs Cairns vs Sydney), using permuted blocks of random sizes. Randomization will occur following enrolment into the study and completion of all baseline

assessments except for 7-day habitual PA monitoring. Table 2 contains information about concealment and blinding (masking), who these apply to, how and when. As participant health and safety is managed directly by Frame Running coaches who are not blind to treatment allocation, procedures for emergency unblinding are not required.

Table 2: Blinding (masking) and concealment information for the Run4Health CP trial

Group or individual blinded	Information withheld	Method of blinding
Person assigning participants to groups	Group assignment	(REDCap®) randomization module, with schedule generated and entered by a biostatistician not otherwise involved in participant recruitment, assessment, or trial conduct. Trial staff with access to the randomization function (to allocate participants) do not have access to the randomization schedule.
Participants	Not blinded after baseline	
Coaches delivering intervention	Not blinded after baseline	
Outcome assessors	Group assignment	Not told of group assignment and no access to randomization status or intervention information on REDCap®. Participants and caregivers will be asked not to discuss their assignment with the outcome assessor. Questionnaires will be entered directly into REDCap® by participants and/or their caregiver and will be locked for editing by study personnel except for one research data manager (who is not on the investigator team) if an error in data entry is made. All changes to data are available in a log accessible from REDCap®.
Research data manager/study coordinator	Not blinded after baseline	
Statistician	Group identity	The analysis code is written and finalised before the dataset is made available for analysis. The groups are randomly assigned as ‘group A’ or ‘group B’ in the downloaded dataset provided to the statistician. The identity of the group is revealed after the primary statistical analysis is complete.
Investigators and manuscript writers	Not blinded	

Data Collection

Interventionist Training and Experience

The interventionists (Frame Running coaches) will be Exercise Physiologists, Physiotherapists and/or Athletics Coaches with at least 2 years' experience prescribing physical activity programs to people with disabilities including CP and conducting group exercise sessions with children and young people. Interventionists will have current cardiopulmonary resuscitation and first aid qualifications and will adhere to institutional policies and procedures for child safety.

Interventionists will be provided with 6 hours face to face didactic training from the Principal Investigator in how to deliver the intervention according to the training manual. The following topics will be covered: (1) general principles of aerobic and anaerobic exercise in CP, (2) coaching principles to provide a fun and intrinsically motivating exercise experience, (3) interpreting and applying the Frame Running intervention manual, (4) correctly fitting athletes to running frames, and (5) practical component. Regular supervision meetings will be conducted throughout the trial to facilitate adherence to the training manual.

Outcome Assessor Training and Experience

Outcome assessors will be Physiotherapists with at least 3 years' experience administering the GMFM-66 to children and youth with CP and will have completed the GMFM Criterion Test for scoring reliability. They will be provided with written and videotaped standardized procedures for the administration of all other study outcome measures. Regular supervision meetings will be conducted to facilitate adherence to the assessment manual.

Retention

Participant Retention

The following strategies will be used to promote participant retention and complete follow-up: (1) Frame Running training will be offered at no cost, (2) where possible according to track availability, sessions will be scheduled at mutually convenient times, (3) questionnaires will be administered using the REDCap® survey module enabling forced choice/completion and automated email reminders, (4) usual care control participants and/or their caregivers will be reminded that a Frame Running participation pack with interventionist follow-up support will be provided after the T3 retention (24 weeks) timepoint is complete, (5) once enrolled, investigators will make all reasonable efforts (including phone call, email and text messages) to contact participants and/or their caregivers to encourage completion of overdue assessments, if any.

Participant Withdrawal

Participants can withdraw at any time. Participants who choose to withdraw from the study will not be penalized in any way. They will be assisted to source another local therapy option that matches their preferences if desired. Participants are informed of their right to withdraw at any time without consequences at the time of reading participant information forms and signing of consent forms. Any de-identified (including re-identifiable) data collected from participants who later withdraw will be retained and included in analyses. Reasons for participant withdrawal will be recorded and reported where available.

Data Management and Access

Study data will be collected and managed using REDCap® (Research Electronic Data Capture) electronic data capture tools hosted at The University of Queensland.[53 54] REDCap is a secure, web-based software platform designed to support data capture for research studies. To promote data quality and minimize data loss, REDCap® forms will be set up with range checks and forced completion. All assessments administered by the outcome assessors for backup if recording forms are incomplete, damaged, or lost. The University of Queensland Research Data Manager database will be used for long term data storage, and a description of the data will be uploaded onto the UQeSpace repository at the conclusion of data collection and analysis. Confidentiality of participant data will be maintained at all times from collection to storage. A de-identified dataset will be made available upon written request for the purposes of further scientific research, including meta-analysis, ancillary studies related to the original aims and objectives, and verification of results.

Statistical Methods

Between-group differences for primary and secondary outcomes will be determined on an intention-to-treat basis using generalized estimating equations to account for the repeated measures design, stratification, and potential missing outcome data.[55] Covariables will be stratification factors (GMFCS II-III vs. IV-V and site), baseline, and wear time for accelerometer data that may be confounded by duration of wear e.g. average minutes per day of sedentary behaviour. Effect estimates will be presented as a mean difference and 95% confidence interval with a significance level of $p<0.05$. Data will be inspected visually for normality, homoscedasticity, and linearity. If any analyses are found to violate necessary assumptions, then data will be transformed, or appropriate non-parametric analysis methods will be utilized.

Data Monitoring and Safety

There are no additional risks to participating in Frame Running beyond typical physical activity participation using adaptive equipment in this population. The following control strategies will be implemented to manage the risk of adverse events: (1) participants will be screened for the presence of comorbid conditions and will be managed by senior experienced clinical staff including the Principal Investigator, (2) families will be provided with an information sheet and brief counselling on the risks associated with wearing accelerometers, with a focus on preventing the development of pressure areas, early identification of allergic skin reactions and reducing unpleasant sensations, (3) treating/assessing staff will be provided with standardized training that includes a component on awareness of risks, application of control strategies and safety, (4) participants may use running frames only with a properly fitting, Australian-standards approved bicycle helmet and appropriate footwear, (5) participants will be reminded to use sun protection and have access to fresh drinking water during training sessions, (6) participants will be instructed on safe use of the running frame at a familiarization session of at least 10 minutes, and (7) fatigue and pain will be monitored on an ongoing basis and training load adapted accordingly. Coaches and assessors are asked to report adverse events in real time using REDCap® which is monitored by the Principal Investigator, who will determine the severity of the adverse event, whether it is expected or unexpected, and whether it is related or unrelated to the intervention. Serious or unexpected adverse events will be discussed at the earliest convenience by the chief investigators (SER, LS, LM, CS, RNB) and reported to the to the Ethics committees, at which point a decision will be made about continuing the trial. No interim analyses will take place. The study is covered by standard clinical trials insurance held by The University of Queensland.

Qualitative Interviews

To fully address the tertiary objective of this study semi-structured interviews will be conducted in up to six focus groups (one participant group and one parent/caregiver group at each site). The aims of the qualitative interviews are to understand how participants and/or their caregivers perceive their involvement in the program, and elucidate barriers and facilitators to ongoing, sustainable participation in Frame Running. Qualitative interview transciption will be completed by a high quality paid service and checked against original recordings. Participants will have the opportunity to review their transcripts and edit their responses prior to analysis. Transcripts will be thematically analysed using an inductive content analysis approach.[56]

Patient and Public Involvement

A person with cerebral palsy, a parent/caregiver, and Frame Running organizations have been invited to participate as consumer representatives during the study period. They will be financially compensated for their time and expertise at the rate of $50 AUD per hour. A parent of a child with cerebral palsy (who participates and competes in Frame Running at an international level) reviewed the protocol and provided feedback on the study design, which has been integrated. At least one consumer representative will meet with the study team not less than every two months once recruitment commences to provide advice and input in relation to all following phases of the trial (conduct, analysis, and reporting).

ETHICS AND DISSEMINATION

Informed Consent Process

For children and youth <18 years of age or ≥18 years with an impaired capacity to consent, written informed consent will be obtained from the legal guardian. Youth ≥18 years who can provide their own written informed consent will do so. This will occur after the treating/assessing staff member has explained the study again in an accessible format (verbal, written) to the satisfaction of both the participating parent/guardian and/or child/youth.

Ethics and Dissemination

Run4Health CP is registered on the Australian New Zealand Clinical Trials Registry (ACTRN12621000317897p). Protocol updates will be reflected in the trial registration and reported in the primary results manuscript. The project has received ethics approval from the Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (HREC/21/QCHQ/69281) and the University of Queensland Human Research Ethics Committee (2021/HE000725). Results of the study will be published/disseminated in (1) the trial registration database, (2) conference abstracts and presentations, (3) peer-reviewed articles in scientific journals, (4) organization and institution newsletters and media releases, and (5) in accordance with the Australian National Statement 3.1.65, directly to participants and consumers in a format that is appropriate and accessible to them as the research will be likely to generate findings or results of significance to young people with CP and their families.

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AUTHOR STATEMENT

SR, LS, LM, CS, EB, KW and RNB conceived the trial. SR completed the initial draft of the manuscript. MC generated the randomization strata and provided biostatistical advice and information. SGT, RT, and ID contributed technical expertise to the protocol manuscript for physical activity measurement, therapist outcome assessment, and Frame Running coaching respectively. AG and BD designed the Frame Running training session content. All authors designed the study, have read, edited, and approved the final manuscript and supplementary files.

FUNDING STATEMENT

The Run4HealthCP trial is financially supported by an Early Career Research Project Support Grant awarded by the Children's Hospital Foundation (grant ID: ECR0262020), and the Merchant Charitable Foundation via the Children's Hospital Foundation (donation ID:

10415). Running frames used in the trial will be borrowed at no cost (except return freight) from various individuals and organisations including the sole supplier.

COMPETING INTERESTS STATEMENT

The authors have no conflicts of interest to declare. The funding sources had no role in the initiation or design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results. This study is investigator-initiated, and therefore the principal investigator and The University of Queensland is the study sponsor and assumes responsibility for the initiation, management, conduct, and analysis of the trial.

KEYWORDS

cerebral palsy, adaptive sports, running, physical fitness, exercise training

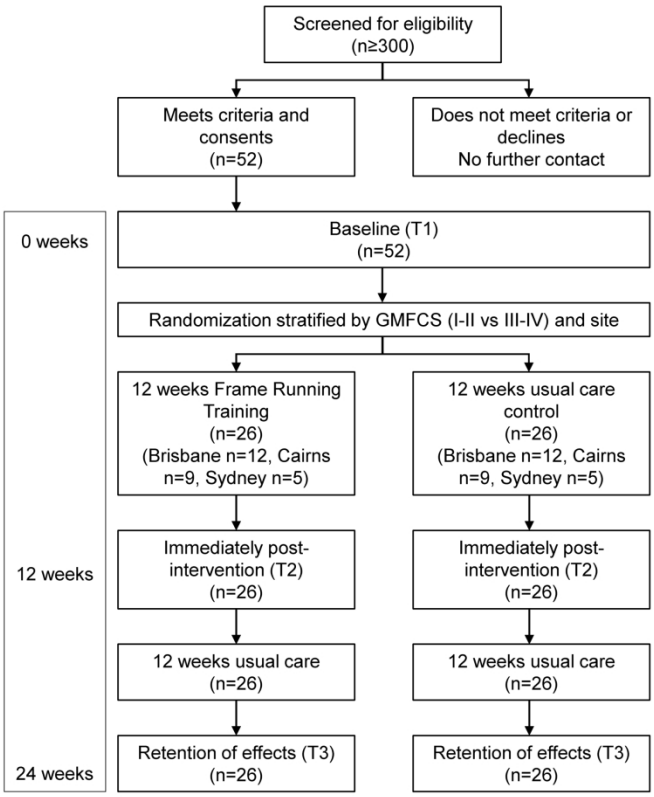
FIGURE LEGENDS

Figure 1: Petra RaceRunner™ By ConnieHansen running frame

Figure 2: Run4Health CP CONSORT study flowchart

Petra RaceRunner™ By ConnieHansen running frame

1156x650mm (72 x 72 DPI)



Run4Health CP CONSORT study flowchart

190x275mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered,	4

		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	#3	Date and version identifier	4
Funding	#4	Sources and types of financial, material, and other support	36
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-2 and 36
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1 and 37
Roles and responsibilities: sponsor and funder	#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	37
Roles and responsibilities: committees	#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)	22, 25, and 26

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	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	9-12
Objectives	#7	Specific objectives or hypotheses	7-8
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, non-inferiority, exploratory)	8 and 21-22
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	8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg,	9 and 23

		surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-12
Interventions: modifications	#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)	12-13
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	12-13
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	14-15
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	15-20
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)	19-20 Figure 2

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	20
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	20-21
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	21-22
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	21-22
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	21-22

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	21-22
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	21-22
Methods: Data collection, management, and analysis			
Data collection plan	#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	15-18 and 23
Data collection plan: retention	#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	24
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality	25

		(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	
Statistics: outcomes	#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	25
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	25
Statistics: analysis population and missing data	#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)	24 and 25
Methods: Monitoring			
Data monitoring: formal committee	#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	26
Data monitoring: interim analysis	#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	26
Harms	#22	Plans for collecting, assessing, reporting, and managing	12-13,

		solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17-18, and 26
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	28
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)	28
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	28
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	25
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	25

		trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	37
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	25
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	24 and 26
Dissemination policy: trial results	#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	28
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	36
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	N/A

	biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

Notes:

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BMJ Open

Study protocol for Running for health (Run4Health CP): a multi-centre, assessor-blinded randomized controlled trial of 12 weeks of twice weekly Frame Running training versus usual care to improve cardiovascular health risk factors in children and youth with cerebral palsy

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-057668.R1
Article Type:	Protocol
Date Submitted by the Author:	25-Feb-2022
Complete List of Authors:	Reedman, Sarah; The University of Queensland, Child Health Research Centre Sakzewski, Leanne; The University of Queensland, Child Health Research Centre McNamara, Lynda; Cairns and Hinterland Hospital and Health Service, Physiotherapy Department Sherrington, Catherine; University of Sydney, Institute for Musculoskeletal Health Beckman, Emma; The University of Queensland, School of Human Movement and Nutrition Sciences West, Kerry; Children's Hospital at Westmead, Physiotherapy Department Trost, Stewart; The University of Queensland, School of Human Movement and Nutrition Sciences Thomas, Rachel; Queensland Children's Hospital, Queensland Paediatric Rehabilitation Service Chatfield, Mark; University of Queensland, Child Health Research Centre Dutia, Iain; The University of Queensland, School of Human Movement and Nutrition Sciences Gennen, Alix; The University of Queensland, Child Health Research Centre Dodds, Bridget; The University of Queensland, Child Health Research Centre Cotton, Zoë; The University of Queensland, Child Health Research Centre Boyd, Roslyn; The University of Queensland, Child Health Research Centre
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Sports and exercise medicine, Paediatrics
Keywords:	Developmental neurology & neurodisability < PAEDIATRICS, SPORTS MEDICINE, REHABILITATION MEDICINE

TITLE

Study protocol for Running for health (Run4Health CP): a multi-centre, assessor-blinded randomized controlled trial of 12 weeks of twice weekly Frame Running training versus usual care to improve cardiovascular health risk factors in children and youth with cerebral palsy

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Word count

6295/4000

ABSTRACT

Introduction

Children and youth with moderate-severe (Gross Motor Function Classification System [GMFCS] levels II-V) cerebral palsy (CP) participate less frequently in physical activities compared to peers without CP and have elevated risk of cardiorespiratory morbidity and mortality in adulthood. Frame Running (RaceRunning) is a new athletics discipline that is an accessible option for physical activity participation for people with moderate-severe CP. There is no high-quality evidence for the effect of Frame Running on cardiovascular disease in children and young people with CP. The primary aim of this study is to conduct a randomized controlled trial of the effect of 12 weeks of Frame Running training on risk factors for cardiovascular disease.

Methods and Analysis

Sixty-two children and youth with CP (age 8-20 years) in GMFCS levels II-V will be recruited across four sites and randomized to receive either 12 weeks of Frame Running training twice weekly for 60 minutes, or usual care. Outcomes will be measured at baseline, immediately post-intervention (primary endpoint), and 12 weeks later for retention of training effects. The primary outcome is cardiorespiratory fitness as measured by distance covered on Six Minute RaceRunner Test (6MRRT) with 1 minute heart rate recovery (HRR_{1min}). Other outcomes include: blood pressure, objectively measured physical activity, body mass index, waist circumference, percentage body fat, gross motor function capacity, community participation, feasibility, tolerability, and safety. Adverse events will be monitored, and participants and their caregivers will be interviewed to discern their experiences of participation in Frame Running.

Ethics and Dissemination

The Children's Health Queensland Hospital and Health Service and the University of Queensland Human Research Ethics Committees have approved this study. Results will be disseminated in peer-reviewed journals and scientific conferences; through professional and athletic organisations; and to people with CP and their families.

Registration

Australian New Zealand Clinical Trials Registry number: ACTRN12621000317897.

ARTICLE SUMMARY

Strengths and limitations of this study

- This randomized controlled trial of Frame Running training in children and youth with cerebral palsy is powered to detect change on the primary outcome measure of cardiovascular fitness.
- Retention (sustainability) of changes will be examined at a follow-up 12 weeks after the training sessions are complete.
- Children and youth with severe functional mobility limitations and intellectual disability will be included.
- A validated maximal exercise test will not be conducted.

INTRODUCTION

One in 700 Australians have cerebral palsy (CP), a permanent but not unchanging disorder of posture and movement caused by a disturbance to the developing foetal or infant brain.[1] Children with CP participate in physical activities less often compared to peers without CP.[2] Children with CP also have high levels of sedentary behaviour,[3] apparent from early infancy and peaking by four to five years of age when followed through to middle childhood.[4] Adults with CP experience increased risk of non-communicable diseases associated with low PA including cardiovascular disease, mental illness, osteoporosis and osteoarthritis (Odds ratios 1.3-5.8).[5] There is evidence that the disparity in non-communicable disease risk begins early, with a large population-based cohort study demonstrating increased risk of mental health disorders in children (6-17 years of age) with CP compared to children without CP.[6] In this study, pain and low physical activity level explained part of the relationship between CP and depression.[6]

Life expectancy in people with CP in general is only slightly reduced compared to the people without CP, however those individuals with moderate-severe motor impairments have significantly lower life expectancy.[7] The causes of early death in people with CP are most frequently respiratory and cardiovascular diseases,[8] with respiratory illness the leading cause of death in children with CP.[9] An Australian prospective population-based register study following n=3507 individuals with CP determined that inability to walk independently (an indicator of severe CP), was the strongest predictor of mortality in people with CP (adjusted hazard ratio 6.2).[10] There is expert consensus that increasing aerobic fitness and PA in children with severe CP is likely to ameliorate the severity of acute respiratory illness.[9] Despite this, recent systematic reviews have demonstrated that there are no effective physical activity interventions for people with CP that do not walk independently, and interventions for children who can walk independently may not have a clinically meaningful effect on

physical activity behaviours including habitual physical activity and participation in physical activities.[11 12] Contributing factors to inefficacy may have included: selection bias (inclusion of children with the highest level of physical activity and physical functioning), failure to address environmental, contextual and behavioural barriers to physical activity, issues with outcome measurement,[11] and dosing below minimum recommended guidelines.[13] It is clear that there is an urgent need for high quality research into physical activity interventions of sufficient dose and duration in youth with CP who have major limitations in walking ability. Furthermore, such interventions need to be safe, community-based, informed by consumer needs, and aimed to enable ongoing, normal community participation and inclusion.

Frame Running, formerly known as RaceRunning, is a para-athletics discipline recently sanctioned by World Para Athletics (the International Paralympic Sports Federation for athletics). Frame Running was invented in 1991 by Connie Hansen, an Occupational Therapist and para-athlete and Mansoor Siddiqi, a para-athlete with CP competing in the now defunct discipline of backward wheelchair racing (foot-propelled). Frame Running utilises a three-wheeled frame with low rolling resistance for support, enabling running in people with otherwise severe mobility limitations (see Figure 1). In the absence of an existing systematic review of the literature, an author search conducted on 21 September 2021 for articles indexed in the PubMed database, using the terms “RaceRunning” OR “Frame Running” OR “race running” AND “cerebral palsy” located in title/abstract (with additional hand search of reference lists for included articles). This search returned only seven studies: one pilot single-group pre-post trial,[14] one study protocol for a pilot randomized feasibility study,[15] one reliability study for a Frame Running-specific field exercise test,[16] two cross-sectional studies examining relationship between impairments and Frame Running performance,[17 18] and two cross-sectional studies on kinesiologic and metabolic responses or adaptations to use of running frames.[19 20] The pre-post pilot trial included n=15 adolescents and young adults with

CP (age range 9-29 years, Gross Motor Function Classification System [GMFCS] levels I-IV) and demonstrated that 12 weeks of twice weekly Frame Running training led to on average, a 34% increase in cardiorespiratory endurance and a 9% increase in thickness of the medial gastrocnemius muscle.[14] Frame Running can evoke a heart rate commensurate with high intensity exercise,[19] and uses large muscle groups in a reciprocal way that may have functional cross over to enhanced mobility.[20] A larger (n=25) pre-post pilot study of once weekly Frame Running training for 24 weeks duration is planned.[15] This study with no accompanying sample size calculation has the potential to be underpowered and/or underdosed to detect improvements in cardiometabolic risk factors. Furthermore, as the study is unrandomized, the quality and certainty of the evidence provided will necessarily be lower than a randomized study.

We therefore aim to conduct an adequately powered randomized controlled trial of Frame Running training in children and youth with CP on cardiometabolic risk factors and related outcomes (Run4Health CP). This study may therefore provide evidence that cardiometabolic risk factors can be modified in children and youth with CP who have moderate to severe motor impairment and high support needs in mobility. This evidence may have critical patient and clinical impacts through support of funding for running frames and may help to foster development of the discipline and expand participation opportunities.

[Insert Figure 1 about here]

METHODS AND ANALYSIS

Objectives

The primary objective of this study is to compare the effect of 12 weeks of Frame Running training versus usual care control on cardiovascular fitness (endurance) on the Six Minute RaceRunner Test (6MRRT) and 1-minute heart rate recovery (HRR_{1min}) following exercise

testing immediately at post-intervention (primary endpoint) and at 12 weeks post-intervention.

Secondary objectives are to compare the effect of 12 weeks of Frame Running training versus usual care control immediately post-intervention and at 12 weeks post-intervention on:

1. other cardiovascular risk factors including: resting blood pressure, habitual physical activity level, body mass index, percent body fat, and waist circumference.
2. gross motor activity capacity including gross motor function and Frame Running-specific activity limitation tests
3. community participation.

The tertiary objective of this study is to determine whether 12 weeks of Frame Running training is feasible, tolerable, safe, and sustainable in the study population, including whether participants report that it induces additional pain and fatigue when compared to usual care.

Trial Design

Run4Health CP is a pragmatic, single (assessor)-blind randomized controlled, multi-centre trial with two parallel groups. The primary timepoint is immediately post-intervention (12 weeks post-baseline) and the secondary timepoint is 12 weeks post-intervention (24 weeks post-baseline). The study will be conducted in four Australian cities, Brisbane (n=24), Cairns (n=18), Sydney (n=10) and Sunshine Coast (n=10). Assessment of outcome measures and Frame Running training will be conducted at community synthetic athletics tracks and nearby associated indoor sports facilities at a time convenient to participants and their caregivers. Recruitment commenced on 16 August 2021 and the first participant was enrolled on 16 September 2021. Last participant data collection is anticipated in January 2023.

Eligibility Criteria

Participants eligible for the trial must comply with all of the following eligibility criteria at randomization: (1) diagnosis of cerebral palsy and classified in GMFCS levels II-V, (2) between 8.00 to 20.99 years of age, (3) live within 150km of one of the trial sites, (4) have not engaged in more than 6 sessions of formal Frame Running training with a coach or health professional within the last 6 months, (5) can understand and follow the directions of the coach and assessors for the purposes of training safely and completing outcome measurement in the opinion of the Principal Investigator.

Participants are excluded if at any time: (1) the child/youth has orthopaedic and/or neurological surgery within 6 months prior to baseline or during the study period requiring a period of recovery that would exclude the participant from training for more than one week, (2) the child/youth has uncontrolled epilepsy, medical fragility, and/or serious precautions not able to be accommodated (e.g. significant history of atraumatic lower limb fractures or sacral pressure injuries etc.) precluding participation in moderate-vigorous intensity Frame Running, (3) caregiver English language skills are not sufficient to understand the study information, provide informed consent and/or complete study questionnaires.

Interventions

Frame Running Training Group

Frame Running training will consist of two, 60-minute sessions per week for 12 consecutive weeks (total dose 24 hours). Established guidelines for aerobic exercise to improve cardiovascular health in typically developing individuals recommend a minimum frequency of three sessions per week.[13] There is evidence however that two sessions per week is adequate in deconditioned individuals with CP to improve aerobic fitness,[13] and this was demonstrated in the pilot pre-post study of Frame Running training by Hjalmarsson et al

(2020).[14] This can likely be attributed to the dose-response relationship between PA and cardiorespiratory outcomes, whereby even small increases in PA in previously inactive individuals can result in clinically meaningful improvements in health.[21] Provision of only two sessions per week may also increase the likelihood that participants can comply with the intervention (considering issues such as time and financial constraints relative to a third session).

Participants will attend Frame Running training in groups of approximately three, matched by age and/or ability if possible. Sessions will be administered by a coach with qualifications in Physiotherapy and/or Exercise Physiology. Participants in the training group are permitted to receive their usual care from non-study providers (as per concomitant care) with no restriction.

Frame Running training sessions will consist of a combination of (1) anaerobic Frame Running (i.e. starts and sprints drills using established athletic training principles), (2), aerobic Frame Running (i.e. steady running working towards ≥15 minutes duration), and (3) task-specific functional training for Frame Running technique and skills (e.g. braking, steering, propulsion strategies, running form, and power). Training sessions will increase in difficulty in a stepwise fashion, with the aim to initially develop basic skills in operating a running frame, working towards maintaining moderate-vigorous exercise intensity throughout a 60-minute session. A training load of 60-75% of peak heart rate can elicit a 9-40% increase in peak aerobic capacity with 2-4 sessions per week for minimum 20 mins in individuals with CP.[13] Based on a literature review of exercise training studies, proposed ideal exercise parameters for individuals with CP are: an intensity between 60–95% of peak heart rate, between 40–80% of the heart rate reserve (HRR), or between 50–65% of VO_{2peak}.[13] To monitor adherence to this exercise intensity, participants will wear a Polar Verity Sense (Polar Electro Oy, Kempele Finland) optical heart rate monitor on the non-dominant upper

limb during training sessions with output observed by the coach and/or assistants (e.g. undergraduate physiotherapy or exercise physiology students). As suggested by Verschuren et al., peak heart rate will be estimated at 194 beats per minute for children and youth with CP in the absence of maximal exercise testing.[22] Therefore, the target heart rate will be between 116-185 beats per minute. Where possible when a participant provides a GPS-enabled smartphone, distance covered and time in motion will be recorded by attachment of the smartphone to the running frame using the Polar Beat phone application (Polar Electro Oy, Kempele Finland).

Running frames are registered in the low-risk Medical Device Class 1 category on the Australian Register of Therapeutic Goods. They are manufactured overseas and are imported to Australia by Dejay Medical and Scientific Pty Ltd. There are currently two brands available in Australia, "RAD - Trike - Disability vehicle, cycle, tricycle, foot-propelled" (ARTG: 345236), and "By Connie Hansen - Disability vehicle, cycle, tricycle, foot-propelled" (ARTG: 309224). Both types of running frames may be used in the trial according to availability and suitability, as the differences between these brands are expected to be superficial considering the context of the trial (novice and beginner Frame Running athletes, recreational style participation with elementary competition). Where possible, the same frame will be used by each participant throughout the study period with consistent attachments, seat height, and chest plate angle/depth unless these are adapted for performance reasons.

Usual Care Control Group

Participants in the control group will receive their usual care from non-study providers (type/dose/content as per concomitant care). This will determine the effect of Frame Running training in addition to usual care, which already contains active treatments such a

physiotherapy and/or occupational therapy. Participants in the control group will not be offered Frame Running training and will be asked to refrain from participating in Frame Running until they have exited the study, however, this will not be actively prevented for ethical reasons. As Frame Running requires access to a running frame, and participants are not expected to have their own frame, it is expected that few participants in the control group will participate in Frame Running during the study period.

Following outcome measurement at the final time point, participants in the control group will be provided with an information package regarding local Frame Running training sessions, running frame fitting results (e.g. frame size required and attachments), and advice about how to obtain a running frame and participate in the sport. They will also receive up to two phone calls from a therapist providing physical activity counselling and advice. The aim of this package of supports is to improve equity in access to Frame Running opportunities for those otherwise receiving a no-treatment control.

Modifications and Adaptations

Heart rate data will be used to adjust the session in real time and to tailor the progression of session difficulty from week to week so that the participant spends at least 60% of session duration in the target HR range. Individual tailoring will also accommodate variability in participants' propulsion strategies, motor type/distribution, activity limitations, age, and interests. If any unexpected, unusual, or additional pain or fatigue beyond what is considered "normal" is experienced by a participant allocated to the Frame Running training group, this will be discussed with the participant and their caregiver and modifications to the training program may be implemented. Unexpected or unusual pain or fatigue in the training group will be recorded as an adverse event. Other participant characteristics may necessitate

modification or adaptation to the training program, including but not limited to intellectual disability, injury, hearing and/or vision impairment, tactile and/or proprioceptive impairment, behavioural and/or emotional dysregulation. Modifications may include reduction in dose, changes to training session content, use of assistive technology (hearing aids, visual aids etc.), visual guides, caregiver involvement, and/or advice and education regarding management of pain, injury and fatigue.

Adherence and Fidelity

The training content has been manualized to facilitate consistent application by coaches across trial sites and participants, and to promote adherence to the prescribed dose. Several strategies will be applied to optimize the participant's frequency of attendance at sessions and level of involvement (which is defined as the subjective experience of participation while attending, and includes elements such as engagement, motivation, persistence, and affect[23]). These strategies are hypothesized to fulfil participants' basic psychological needs of autonomy, competence and relatedness according to Self-Determination Theory,[24] which has been demonstrated to underpin physical activity interventions in children with CP[25]:

1. Training activities will be individually tailored as described above. This is likely to facilitate a "just right challenge" and fulfil participants' need for competence.[25]
2. Training will occur in groups of approximately three, matched where possible for age and/or ability. Training together with peers, with social group dynamics managed carefully, is likely to promote social connection and fulfil participants' need for relatedness.[26]

3. Coaches will use autonomy-supportive, empathetic communication with participants and families. Coaches will facilitate participant self-efficacy through teaching positive self-talk about performance and will promote positive peer to peer encouragement.[25]

Furthermore, training sessions will take place in locations where Frame Running squads train on a regular basis. This provides an ongoing avenue for normal, regular participation in the sport once the free clinical trial sessions conclude.

Individual adherence to the training manual will be recorded on a session-by-session basis by coaches. Measures include:

1. Percentage of sessions attended (including partial attendance).
2. Percentage of training drills completed according to the manualized content.
3. Percentage of session duration spent within the target heart rate threshold for training intensity.
4. List of modifications or adaptations.
5. Distance covered and time in motion during the training session.

Reasons for missed or incomplete sessions will be recorded. Adherence data will be reported alongside study outcomes.

Concomitant Care

Participants in both groups may continue any usual care from non-study providers throughout the study period (except Frame Running in the usual care control group). Type, dose and duration of usual care is likely to vary widely between participants owing to individual needs, access, and funding arrangements. This could include Botulinum Toxin-A injections, serial casting, and a broad array of exercise and movement-based therapies. Participants in both

groups will be asked to record frequency of participation in Frame Running and other physical activities, and frequency/type/dose of usual care therapies from non-study providers from allocation to exit using a Usual Care Diary. Botulinum Toxin-A injections and serial casting are not expected to have significant impacts on our activity and participation-level outcome measures at the group level. Based on prior experience in randomized controlled trials administered by our centre, it is not feasible to exclude participants receiving these interventions as timely recruitment would be affected.

Outcomes

Primary Outcome

Cardiovascular health (primary)

Distance (metres) covered in the Six Minute RaceRunner Test (6MRRT).[16] The 6MRRT is a validated measure of RaceRunning endurance with good test-retest reliability (ICC=0.78-0.91) in children classified in GMFCS levels III and IV. The 6MRRT is theoretically a submaximal exercise test, however it is likely that many participants will achieve almost maximal heart rate.

Secondary Outcomes

Cardiovascular health (secondary)

Heart Rate Recovery in 1 minute (HRR_{1min}) will be taken immediately following the 6MRRT. HRR_{1min} in beats per minute is the difference between the heart rate taken at the cessation of the 6MRRT and exactly 60 seconds later, while the participant is engaged in relative rest (i.e. has stopped moving).[27] HRR_{1min} is strongly associated with cardiac mortality and is responsive to a 12-week cardiac rehabilitation program in children following heart

surgery.[27] Children and youth will wear a Polar Verity Sense Optical heart rate monitor on the less-impaired upper arm during testing.

Resting blood pressure will be measured using an automated arm-cuff sphygmomanometer (valid and reliable).[28] Resting systolic and diastolic Blood Pressure (BP) in mmHg is a traditional risk factor for cardiometabolic disease in individuals with CP,[28] and systolic BP is associated with cardiorespiratory fitness, central adiposity and BMI in children with CP.[29] Systolic and diastolic BP were responsive to a 12-week training program in youth with Down Syndrome.[30]

Habitual physical activity will be quantified using accelerometry, a valid, reliable and feasible method in youth with moderate to severe CP.[31] Participants will wear an ActiGraph GT3X+ on the less-impaired wrist and less-impaired anterior thigh for 7 days during waking hours during their usual activities (free-living). Data will be processed to identify time spent in different postures and activities using machine learning algorithms; a combined thigh and wrist classification model has been validated in children classified in GMFCS levels III and IV.[31]

Body mass index (BMI, kg/m^2) will calculated according to the equation: BMI = weight (Kg)/height^2 (m). Weight will be taken using the same calibrated digital scale at each site and height taken using the same stadiometer at each site for all participants. Participants that are unable to stand unassisted will access chair scales. If body shape distortion is severe and/or standing height is not feasible, then height will be measured using a recumbent measuring board if available or will be estimated using segmental limb length (knee height).[32] Anthropometric measures will be converted to Z-scores using age and gender specific reference data for the general population.[33]

Waist circumference (cm) will be measured to the nearest millimetre at the midline level (midway between the superior border of the iliac crest and the inferior rib margin, often slightly above the umbilicus) using a non-stretchable tape measure.[34]

Percentage body fat will be estimated based on the triceps and subscapular skinfold thickness using CP-specific equations.[35] This will be measured using calipers (Harpenden Skinfold Caliper, Baty International, West Sussex UK) by trained investigators.

Gross motor capacity

Gross motor function will be assessed using GMFM-66, a criterion referenced observation measure developed using Rasch modelling to measure gross motor function of children with CP.[36] The GMFM-66 has established construct validity, high test-retest reliability (ICC 0.99) and is responsive to change.[36 37]

Frame Running-specific activity limitation will be assessed using 100 metre sprint (time in seconds), distance covered in four strides (metres, average of best two trials of three), and step count in 20 metres (steps, average of best two trials of three). The assessment of function is activity specific and therefore outcomes should be strongly related to the activity of interest.[38] These assessments are investigator-developed and will be subject to further independent assessment of their validity and reliability.

Participation

Community participation will be evaluated using the Participation and Environment Measure for Children and Youth (PEM-CY).[39] The PEM-CY is a caregiver-report questionnaire with good test-retest reliability and internal consistency.[39] Youth 18 years and older will be invited

to self-report the questionnaire. Summary scores for participation frequency, involvement, and percent environmental supportiveness will be calculated.

Feasibility, tolerability and safety

Feasibility, tolerability and safety will be measured on a weekly basis in both groups using the Wong-Baker FACES® rating scale (pain),[40] Fatigue Severity Scale (FSS, fatigue),[41] and for the training group only, training load (Rate of Perceived Exertion [RPE] on the OMNI RPE[42] multiplied by session duration).[43] Monitoring of adverse and unintended events including injuries will be undertaken throughout the study.

Classification systems and demographic characteristics

The following validated classification systems will be applied: Gross Motor Function Classification System Expanded and Revised (GMFCS),[44] Manual Abilities Classification System (MACS),[45] Communication Function Classification System (CFCS),[46] Visual Function Classification System (VFCS),[47] Eating and Drinking Ability Classification System (EDACS).[48] The VFCS and EDACS will be applied owing to the contribution of the visual system to athletic performance,[49] and the association between eating and drinking ability and nutrition status, which is relevant to body composition, muscle mass, functional ability and performance in training programs in people with CP.[50 51] If known, the participant's Frame Running Sport Class under the two existing classification systems will be recorded (RR1/RR2/RR3 and/or T71/T72). If unknown (or not yet classified), a provisional classification will be performed following the process outlined by Athletics Australia.

The following participant demographic characteristics will be collected to characterize the sample: participant age, sex, dominant hand, self-reported household income, residential postal code, presence of comorbid diagnoses, list of up to nine sports/PAs the participant attended in the last 12 months, and caregiver frequency of participation in structured and unstructured sports/PAs in the last four months. Participants will also be screened for medical conditions that may be precautions to high intensity exercise using a running frame requiring attention or adaptation but not meeting exclusion criteria (e.g. known stable cardiovascular or respiratory condition etc.).

Participant Timeline

Run4Health CP schedule of assessments and interventions are provided below in Table 1 and the CONSORT[52] study flow diagram is provided in Figure 2.

Table 1: Schedule of assessments for Run4Health CP study.

TIMEPOINT	Enrolment	Allocation/ Baseline	Intervention	Immediately post-intervention (12 weeks)	Retention (24 weeks)
VISIT NUMBER:	Screen	T1		T2	T3
Participant contact	X				
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
Frame running training			X		
Usual care control			X		

ASSESSMENTS:					
Classification systems (GMFCS, MACS, CFCS, VFCS, EDACS)		X			
Demographic questionnaire		X			
Frame Running provisional sport class		X			
Six minute RaceRunner test (6MRRT)		X		X	X
Heart rate recovery in 1 minute (HRR_{1min})		X		X	X
Resting blood pressure		X		X	X
7-day free-living accelerometry for habitual physical activity (ActiGraphGT3X+ thigh and wrist)		X		X	X
Body Mass Index (BMI)		X		X	X
Percent body fat		X		X	X
Waist circumference		X		X	X
Gross Motor Function Measure 66 (GMFM-66)		X		X	X
Frame Running activity limitation tests		X		X	X
Participation and Environment Measure for Children and Youth (PEM-CY)		X		X	X
Wong-Baker FACES rating		X	X	X	X
Fatigue severity scale (FSS)		X	X	X	X
Monitoring of adverse and unintended events		X	X	X	X
Usual care diary		X	X	X	X

[Insert Figure 2 about here]

Sample Size

Based on the primary outcome of 6MRRT which has a smallest detectable difference of approximately 150m and sample SD of 150m,[16] a sample size of n=44 will detect at least this difference at 90% power and two sided 5% significance level. To allow for up to 15% attrition, n=52 (n=26 per group) will be required, however additional funding awarded to increase the implementation of Frame Running in a fourth site (Sunshine Coast) will allow for up to n=62 participants.

Recruitment

Strategies to achieve adequate participant enrolment to reach the target sample size are as follows:

1. Clinical database: potential participants will be identified on a clinical database held and maintained by the Queensland Paediatric Rehabilitation Service (QPRS) at the Queensland Children's Hospital and the Sydney Children's Hospitals Network (SCHN). Caregivers of children/youth who have previously consented to receive communications about research studies will be sent a copy of the study flyer to their contact email or postal address.
2. Clinical service: Children and youth with cerebral palsy attending an associated clinical service within QPRS and SCHN will be identified by their treating clinicians based on eligibility criteria. Clinicians will ask permission to discuss the project and gain consent from the family to be contacted by a project staff member.
3. Patient advertising: Patient waiting areas at associated clinical services within QPRS and SCHN will display the approved flyer during the recruitment period.
4. Newsletter: The flyer will be included in the newsletters distributed by associated clinical services within QPRS and SCHN and research groups of the investigators.
5. Websites: The flyer will be posted on the research websites of the investigators.

6. Social media/word of mouth: The flyer will be posted on social media websites which may include but are not limited to Facebook, Twitter, and Instagram. The electronic version of the flyer may then be shared by third parties.

Allocation and Blinding (Masking)

Participants will be randomly assigned to either Frame Running training or usual care control with a 1:1 allocation as per a computer-generated randomization schedule using the Research Electronic Data Capture (REDCap®) randomization module, stratified by GMFCS (II-III/IV-V) and site (Brisbane vs Cairns vs Sydney vs Sunshine Coast), using permuted blocks of random sizes. Randomization will occur following enrolment into the study and completion of all baseline assessments except for 7-day habitual PA monitoring. Table 2 contains information about concealment and blinding (masking), who these apply to, how and when. As participant health and safety is managed directly by Frame Running coaches who are not blind to treatment allocation, procedures for emergency unblinding are not required.

Table 2: Blinding (masking) and concealment information for the Run4Health CP trial

Group or individual blinded	Information withheld	Method of blinding
Person assigning participants to groups	Group assignment	(REDCap®) randomization module, with schedule generated and entered by a biostatistician not otherwise involved in participant recruitment, assessment, or trial conduct. Trial staff with access to the randomization function (to allocate participants) do not have access to the randomization schedule.
Participants	Not blinded after baseline	
Coaches delivering intervention	Not blinded after baseline	
Outcome assessors	Group assignment	Not told of group assignment and no access to randomization status or intervention information on REDCap®. Participants and caregivers will be asked not to discuss their

		assignment with the outcome assessor. Questionnaires will be entered directly into REDCap® by participants and/or their caregiver and will be locked for editing by study personnel except for one research data manager (who is not on the investigator team) if an error in data entry is made. All changes to data are available in a log accessible from REDCap®.
Research data manager/study coordinator	Not blinded after baseline	
Statistician	Group identity	The analysis code is written and finalised before the dataset is made available for analysis. The groups are randomly assigned as 'group A' or 'group B' in the downloaded dataset provided to the statistician. The identity of the group is revealed after the primary statistical analysis is complete.
Investigators and manuscript writers	Not blinded	

Data Collection

Assessment order

Assessments will be delivered in a standardized order across two sessions (first lab-based, second track-based) on different days to reduce the effect of fatigue and enable a familiarization session with the running frame prior to track-based assessments. The track-based assessments will be delivered in the following order: 100m sprint, distance in four strides, step count in 20m, and 6MRRT with adequate rest in between.

Interventionist Training and Experience

The interventionists (Frame Running coaches) will be Exercise Physiologists, Physiotherapists and/or Athletics Coaches with at least 2 years' experience prescribing physical activity programs to people with disabilities including CP and conducting group exercise sessions with children and young people. Interventionists will have current

cardiopulmonary resuscitation and first aid qualifications and will adhere to institutional policies and procedures for child safety.

Interventionists will be provided with 6 hours face to face didactic training from the Principal Investigator in how to deliver the intervention according to the training manual. The following topics will be covered: (1) general principles of aerobic and anaerobic exercise in CP, (2) coaching principles to provide a fun and intrinsically motivating exercise experience, (3) interpreting and applying the Frame Running intervention manual, (4) correctly fitting athletes to running frames, and (5) practical component. Regular supervision meetings will be conducted throughout the trial to facilitate adherence to the training manual.

Outcome Assessor Training and Experience

Outcome assessors will be Physiotherapists with at least 3 years' experience administering the GMFM-66 to children and youth with CP and will have completed the GMFM Criterion Test for scoring reliability. They will be provided with written and videotaped standardized procedures for the administration of all other study outcome measures. Regular supervision meetings will be conducted to facilitate adherence to the assessment manual.

Retention

Participant Retention

The following strategies will be used to promote participant retention and complete follow-up: (1) Frame Running training will be offered at no cost, (2) where possible according to track availability, sessions will be scheduled at mutually convenient times, (3) questionnaires will be administered using the REDCap® survey module enabling forced choice/completion

and automated email reminders, (4) usual care control participants and/or their caregivers will be reminded that a Frame Running participation pack with interventionist follow-up support will be provided after the T3 retention (24 weeks) timepoint is complete, (5) once enrolled, investigators will make all reasonable efforts (including phone call, email and text messages) to contact participants and/or their caregivers to encourage completion of overdue assessments, if any.

Participant Withdrawal

Participants can withdraw at any time. Participants who choose to withdraw from the study will not be penalized in any way. They will be assisted to source another local therapy option that matches their preferences if desired. Participants are informed of their right to withdraw at any time without consequences at the time of reading participant information forms and signing of consent forms. Any de-identified (including re-identifiable) data collected from participants who later withdraw will be retained and included in analyses. Reasons for participant withdrawal will be recorded and reported where available.

Data Management and Access

Study data will be collected and managed using REDCap® (Research Electronic Data Capture) electronic data capture tools hosted at The University of Queensland.[53 54] REDCap is a secure, web-based software platform designed to support data capture for research studies. To promote data quality and minimize data loss, REDCap® forms will be set up with range checks and forced completion. All assessments administered by the outcome assessors for backup if recording forms are incomplete, damaged, or lost. The University of Queensland Research Data Manager database will be used for long term data storage, and a

description of the data will be uploaded onto the UQeSpace repository at the conclusion of data collection and analysis. Confidentiality of participant data will be maintained at all times from collection to storage. A de-identified dataset will be made available upon written request for the purposes of further scientific research, including meta-analysis, ancillary studies related to the original aims and objectives, and verification of results.

Statistical Methods

Between-group differences for primary and secondary outcomes will be determined on an intention-to-treat basis using generalized estimating equations to account for the repeated measures design, stratification, and potential missing outcome data.[55] Covariables will be stratification factors (GMFCS II-III vs. IV-V and site), baseline, and wear time for accelerometer data that may be confounded by duration of wear e.g. average minutes per day of sedentary behaviour. Effect estimates will be presented as a mean difference and 95% confidence interval with a significance level of $p<0.05$. Data will be inspected visually for normality, homoscedasticity, and linearity. If any analyses are found to violate necessary assumptions, then data will be transformed, or appropriate non-parametric analysis methods will be utilized.

Data Monitoring and Safety

There are no additional risks to participating in Frame Running beyond typical physical activity participation using adaptive equipment in this population. The following control strategies will be implemented to manage the risk of adverse events: (1) participants will be screened for the presence of comorbid conditions and will be managed by senior experienced clinical staff including the Principal Investigator, (2) families will be provided with an

information sheet and brief counselling on the risks associated with wearing accelerometers, with a focus on preventing the development of pressure areas, early identification of allergic skin reactions and reducing unpleasant sensations, (3) treating/assessing staff will be provided with standardized training that includes a component on awareness of risks, application of control strategies and safety, (4) participants may use running frames only with a properly fitting, Australian-standards approved bicycle helmet and appropriate footwear of their choice including orthoses if preferred (same footwear to be worn for all assessments), (5) participants will be reminded to use sun protection and have access to fresh drinking water during training sessions, (6) participants will be instructed on safe use of the running frame at a familiarization session of at least 30 minutes, (7) participants will be encouraged to wear padded bike pants to reduce discomfort in the saddle, and (8) fatigue and pain will be monitored on an ongoing basis and training load adapted accordingly. Coaches and assessors are asked to report adverse events in real time using REDCap® which is monitored by the Principal Investigator, who will determine the severity of the adverse event, whether it is expected or unexpected, and whether it is related or unrelated to the intervention. Serious or unexpected adverse events will be discussed at the earliest convenience by the chief investigators (SER, LS, LM, CS, RNB) and reported to the to the Ethics committees, at which point a decision will be made about continuing the trial. No interim analyses will take place. The study is covered by standard clinical trials insurance held by The University of Queensland.

Qualitative Interviews

To fully address the tertiary objective of this study semi-structured interviews will be conducted in up to eight focus groups (one child/youth participant group and one parent/caregiver group at each site). Participants 18 years or older who provide independent

consent to participate in the intervention will be asked if they would like the option of a parent/caregiver or support person to attend the parent/caregiver group. The aims of the qualitative interviews are to understand how participants and/or their caregivers perceive their involvement in the program, and elucidate barriers and facilitators to ongoing, sustainable participation in Frame Running. Qualitative interview transciption will be completed by a high quality paid service and checked against original recordings. Participants will have the opportunity to review their transcripts and edit their responses prior to analysis. Transcripts will be thematically analysed using an inductive content analysis approach.[56]

Patient and Public Involvement

A person with cerebral palsy, a parent/caregiver, and Frame Running organizations have been invited to participate as consumer representatives during the study period. They will be financially compensated for their time and expertise at the rate of $50 AUD per hour. A parent of a child with cerebral palsy (who participates and competes in Frame Running at an international level) reviewed the protocol and provided feedback on the study design, which has been integrated. At least one consumer representative will meet with the study team not less than every two months once recruitment commences to provide advice and input in relation to all following phases of the trial (conduct, analysis, and reporting).

ETHICS AND DISSEMINATION

Informed Consent Process

For children and youth <18 years of age or ≥18 years with an impaired capacity to consent, written informed consent will be obtained from the legal guardian. Youth ≥18 years who can provide their own written informed consent will do so. This will occur after the

treating/assessing staff member has explained the study again in an accessible format (verbal, written) to the satisfaction of both the participating parent/guardian and/or child/youth.

Ethics and Dissemination

Run4Health CP is registered on the Australian New Zealand Clinical Trials Registry (ACTRN12621000317897). Protocol updates will be reflected in the trial registration and reported in the primary results manuscript. The project has received ethics approval from the Children's Health Queensland Hospital and Health Service Human Research Ethics Committee (HREC/21/QCHQ/69281) and the University of Queensland Human Research Ethics Committee (2021/HE000725). Results of the study will be published/disseminated in (1) the trial registration database, (2) conference abstracts and presentations, (3) peer-reviewed articles in scientific journals, (4) organization and institution newsletters and media releases, and (5) in accordance with the Australian National Statement 3.1.65, directly to participants and consumers in a format that is appropriate and accessible to them as the research will be likely to generate findings or results of significance to young people with CP and their families. The study will be reported in a way consistent with both Template for Intervention Description and Replication (TIDieR)[57] and Consensus on Exercise Reporting Template (CERT) guidelines.[58]

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AUTHOR STATEMENT

SR, LS, LM, CS, EB, KW and RNB conceived the trial. SR completed the initial draft of the manuscript. MC generated the randomization strata and provided biostatistical advice and information. SGT, RT, and ID contributed technical expertise to the protocol manuscript for physical activity measurement, therapist outcome assessment, and Frame Running coaching respectively. AG and BD designed the Frame Running training session content. ZC designed

the assessment methods and procedures. All authors designed the study, have read, edited, and approved the final manuscript and supplementary files.

FUNDING STATEMENT

The Run4HealthCP trial is financially supported by an Early Career Research Project Support Grant awarded by the Children's Hospital Foundation (grant ID: ECR0262020), the Merchant Charitable Foundation via the Children's Hospital Foundation (donation ID: 10415), and the Dr June Canavan Foundation via the Children's Hospital Foundation. Running frames used in the trial will be borrowed at no cost (except return freight) from various individuals and organisations including the sole supplier.

COMPETING INTERESTS STATEMENT

The authors have no conflicts of interest to declare. The funding sources had no role in the initiation or design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results. This study is investigator-initiated, and therefore the principal investigator and The University of Queensland is the study sponsor and assumes responsibility for the initiation, management, conduct, and analysis of the trial.

KEYWORDS

cerebral palsy, adaptive sports, running, physical fitness, exercise training

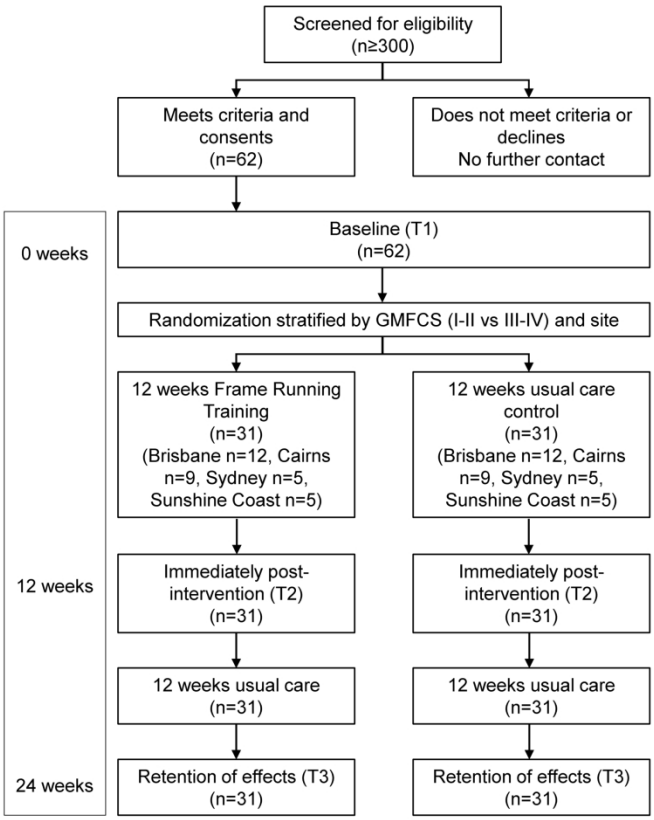
FIGURE LEGENDS

Figure 1: Petra RaceRunner™ By ConnieHansen running frame

Figure 2: Run4Health CP CONSORT study flowchart

Petra RaceRunner™ By ConnieHansen running frames

134x90mm (300 x 300 DPI)



Run4Health CP CONSORT study flowchart

190x275mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered,	4

		name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	4
Protocol version	#3	Date and version identifier	4
Funding	#4	Sources and types of financial, material, and other support	36
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1-2 and 36
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	1 and 37
Roles and responsibilities: sponsor and funder	#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	37
Roles and responsibilities: committees	#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)	22, 25, and 26

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	5-7
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	9-12
Objectives	#7	Specific objectives or hypotheses	7-8
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, non-inferiority, exploratory)	8 and 21-22
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	8
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg,	9 and 23

		surgeons, psychotherapists)	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9-12
Interventions: modifications	#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)	12-13
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	12-13
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	14-15
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	15-20
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)	19-20 Figure 2

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	20
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	20-21
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	21-22
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	21-22
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	21-22

Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	21-22
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	21-22
Methods: Data collection, management, and analysis			
Data collection plan	#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	15-18 and 23
Data collection plan: retention	#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	24
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality	25

		(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	
Statistics: outcomes	#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	25
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	25
Statistics: analysis population and missing data	#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)	24 and 25
Methods: Monitoring			
Data monitoring: formal committee	#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	26
Data monitoring: interim analysis	#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	26
Harms	#22	Plans for collecting, assessing, reporting, and managing	12-13,

		solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17-18, and 26
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	28
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)	28
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	28
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	25
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	25

		trial	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	37
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	25
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	24 and 26
Dissemination policy: trial results	#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	28
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	36
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	25
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of	N/A

	biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable

Notes:

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