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# Progressive resistance training in young people with Prader-Willi syndrome: protocol for a randomised trial (PRESTO)



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**TITLE:** Progressive resistance training in young people with Prader-Willi syndrome: protocol for a randomised trial (PRESTO)

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## ABSTRACT

**Introduction:** Prader-Willi Syndrome (PWS) is a rare genetic condition that results in muscle weakness and low muscle tone. Preliminary evidence suggests progressive resistance training may be beneficial for people with PWS.

**Methods and analysis:** This multisite, randomised controlled trial, with an embedded health economic evaluation and process evaluation, will investigate the effectiveness and cost-effectiveness of progressive resistance training for people with PWS. Sixty participants with PWS will be recruited across Australia and randomised to receive either progressive resistance training (experimental) or non-progressive exercise (placebo-control). Participants will be aged 13 to 60 years, be able to follow simple instructions in English, and have no contraindications to performing progressive resistance training. Participants randomised to the experimental group will receive a progressive resistance training program twice weekly for 24 weeks supervised by an exercise professional at a community gym. Participants in the control group will receive all aspects of the experimental intervention except progressive overload. Outcomes will be assessed at week 25 (primary endpoint) and week 52 by a blinded assessor. The primary outcome is muscle strength assessed using one repetition maximum for upper limb and lower limb. Secondary outcomes are muscle mass, functional strength, physical activity, community participation, health-related quality of life and behaviour. Health economic analysis will evaluate cost-effectiveness. Process evaluation will assess the safety and fidelity of the intervention, investigate mechanism of impact and explore participant experiences and contextual factors affecting implementation.
**Ethics and dissemination**: Ethical approval was obtained from The Royal Children's Hospital Human Research Ethics Committee (HREC/50874/RCHM-2019) under the National Mutual Acceptance initiative. Research governance approvals were obtained from The Royal Children's Hospital, Melbourne; Royal Prince Alfred Hospital, Sydney; Queensland Children's Hospital, Brisbane; Princess Alexandra Hospital, Brisbane; and Austin Hospital, Melbourne. Results will be disseminated through published manuscripts, conference presentations, public seminars and practical resources for stakeholder groups.

**Trial registration** Australian and New Zealand Clinical Trial Registry (ACTRN12620000416998).


**Strengths and limitations of this study:**

- Multisite randomised controlled trial recruiting participants from across Australia to investigate the effectiveness of progressive resistance training for people with Prader-Willi Syndrome on muscle strength (primary outcome), muscle mass, functional strength, physical activity, behaviour and participation.
- Inclusion of an embedded health economic analysis will evaluate cost-effectiveness of progressive resistance training from healthcare and societal perspectives, with outcomes based on muscle strength (primary outcome) and health-related quality of life (secondary outcome).
- An embedded process evaluation will assess intervention safety and fidelity, mechanism of impact, participant experiences and contextual factors affecting implementation.
- Participants will be blinded to group allocation, however it is not possible to blind exercise professionals.

## INTRODUCTION

Prader-Willi syndrome (PWS) is a rare condition with extensive musculoskeletal sequelae resulting from a genetic abnormality on chromosome 15 at q11–13.[1] Approximately 400,000 people live with PWS worldwide.[2] In combination with hyperphagia (uncontrolled urge to eat), intellectual disability,[3] emotional outbursts[4] and anxiety,[5] PWS can result in premature death[6] due to extreme obesity.[7, 8] Limited treatments exist and health care costs are high; estimated in 2016 to be €60k per individual per annum.[9,10,11]

The musculoskeletal features of PWS include abnormal growth and body composition.[12] People with PWS have very low lean body mass, muscle weakness and hypotonia. Their muscle mass is 25 to 40% lower and their muscle strength approximately 70% lower than those without PWS. This has detrimental effects on physical functioning, causing severe delay in childhood motor development and persistent mobility problems in adulthood.[12] Approximately 90% of people with PWS require assistance with activities of daily living.[13] For people with PWS, muscle weakness, hypotonia and poor motor proficiency can reduce the desire to be active,[14] leading to a cycle of sedentary behaviour, deteriorating muscle function, obesity, greater metabolic risk, social isolation, lower quality of life,[15] and early mortality.[3] Increasing muscle strength has the potential to improve mobility, making it easier to perform activities of daily living, and increasing physical activity.

The musculoskeletal features of PWS also adversely impact metabolic function. Having very low muscle mass limits the ability to balance increased energy intake due to hyperphagia, making weight control difficult. Medications to increase muscle mass are either ineffective[16] or expensive. Usual care in PWS comprises aerobic exercise and a strictly controlling diet. However, aerobic exercise targets cardiovascular fitness rather than increases in muscle strength or muscle mass and so does not directly address altered body composition. Aerobic exercise also requires coordination, concentration and time commitment, which can affect adherence and make it difficult for those with mobility problems, complex behavioural issues and intellectual disability.

Muscle strength and muscle mass are increased by progressive resistance training (strength training) in the general[17] and other disability populations,[18] when implemented with sufficient intensity and progression of load.[19] No trials have investigated the effect of progressive resistance training in people with PWS, so it is unclear if it will have the intended effect given the genetic basis to their muscle weakness (their muscles may not adapt to training) and their complex behavioural issues could be a substantial threat to regular exercise adherence. Progressive resistance training requires high loads to be lifted for a low number of repetitions before muscular fatigue, with load progression as the person gets stronger. Preliminary evidence from three small studies in children[20, 21] and adults with PWS,[22] demonstrate proof-of-principle that muscle strengthening exercise can increase strength[22] and muscle mass,[20,21] leading to improvements in walking[22] and physical activity.[20] However, in these studies the training was usually not progressed; was home-based requiring parental supervision; and, the research designs lacked rigour due to no randomisation, control groups, or blinded assessment. A recent randomised feasibility trial ($n$=16) of a 10-week program supervised by a physiotherapist successfully implemented progressive resistance training with excellent attendance (92%) and adherence (82%) and few minor adverse events.[23] Estimates of effect were moderate to large in favour of progressive resistance training compared to a waitlist control group. A qualitative study conducted alongside the trial found the supervising physiotherapists perceived progressive resistance training fostered independence and

confidence in the participants with PWS. Thus, increasing muscle strength in young people with PWS could mean less need for assistance with activities of daily living (reducing carer burden and costs) and improved ability to participate in physical activity, improving health and reducing obesity-related comorbidity.

Therefore, our primary aim is to establish if 6-months community-based progressive resistance training is effective in improving the arm and leg muscle strength of people with PWS. Our secondary aims are to:
(i) determine if progressive resistance training leads to changes in muscle mass, functional strength physical activity, community participation, health-related quality of life and behaviour;
(ii) determine if progressive resistance training is cost-effective in people with PWS; and
(iii) complete a process evaluation that assesses intervention safety and fidelity, explores mechanisms of impact, understands participant experiences, explores contextual factors affecting implementation and identifies pragmatic strategies for successful implementation of progressive resistance training in those with intellectual disabilities and behavioural challenges.

## METHODS AND ANALYSIS

### Trial design

A multisite, parallel-group randomised controlled trial (RCT) with follow-up at one year, and embedded health economic and process evaluations, will be conducted. Participants with PWS will be randomly allocated to either the experimental group (progressive resistance training) or a placebo-control group (non-progressive exercise) (Fig 1). Randomisation will be in a 1:1 ratio with stratification by trial location (VIC, NSW or QLD) and minimisation (by age, sex, type of PWS and receipt of growth hormone therapy) with a random component of 80%. Randomisation will occur after eligibility has been determined, the participant has consented, and a baseline assessment completed. Randomisation will be coordinated by Griffith University Randomisation Service, Queensland, Australia. The trial has been registered prospectively, including updates, with the Australian and New Zealand Clinical Trial Registry (online supplemental appendix 1).

### Participants

To be eligible for inclusion, participants must meet the following criteria:
(1) have genetically confirmed PWS, and live in Australia;
(2) aged between 13 and 60 years; andf
(3) able to follow verbal instructions in English.

People will be excluded if they:
(1) have participated in progressive resistance training in the 3 months prior to randomisation; or,
(2) have a concurrent physical or mental health condition (e.g., severe arthritis, severe psychosis, physically aggressive behaviour) affecting their ability to participate in community-based exercise.

### Recruitment

Participants will be recruited through four sources:

(i) Population registries or clinical databases (e.g. Victorian PWS register; Global PWS Registry; and the Australian National PWS database). Custodians of these databases will send a copy of the trial advertisement to potential participants.
(ii) Specialist PWS clinics in Melbourne, Sydney, and Brisbane. Potential participants will be informed of the trial by their treating doctor or therapist.
(iii) PWS advocacy groups based in Australia will send a copy of the flyer advertising the trial to their members.
(iv) Parent and carer networks (including social media groups): research team members who are parents of people with PWS will disseminate information about the trial to their personal networks and through parent and carer forums.

Prospective participants or their caregiver will complete a screening process by telephone with a research team member to assess their eligibility for the trial, including the completion of a pre-exercise screening questionnaire (PAR-Q+).[24] If any concerns related to suitability to take part are identified, they will be asked to obtain medical clearance prior to enrolment (e.g. unexplained symptoms such as chest pain or shortness of breath at rest).

**Intervention**
All participants will continue to receive their usual health care, which will be documented. All participants will complete an exercise program and will be blinded to their group allocation.

*Experimental group*
Participants allocated to the experimental group will complete progressive resistance training twice a week for 24 weeks at a community gymnasium (Table 1). The program, designed according to American College of Sports Medicine guidelines,[17] will comprise 6 exercises: 3 for the upper limbs (e.g. lat pull down) and 3 for the lower limbs (e.g. seated calf raise). Exercises will be performed on pin-loaded weight machines, as these are safer for novices than free weights. Exercises can be modified to suit the availability of equipment at a particular gym. Participants will perform up to 3 sets of 12 repetitions of each exercise until fatigue (intensity of 60-80% of 1 repetition maximum, 1RM). A 2-minute rest will be taken between each set to allow recovery, and resistance will be increased when 3 sets of 12 repetitions of an exercise can be completed. Each training session will last approximately one hour.

Participants will be supervised 1:1 by an exercise professional (Table 1). Supervision will ensure participants exercise at the correct intensity, provide physical and motivational support, and limit participant access to food.[25] The supervising professional will document the program in an online exercise logbook (including exercises performed, weight lifted, number of repetitions and sets). Supervisors will be invited to participate based on their location. They will receive training on the trial protocol, specialist advice on PWS, facilitating exercise in people with PWS, communication strategies, and proactively managing PWS behaviours such as emotional outbursts. The supervisor training will be delivered via a university online learning site and a printed training manual.

Table 1. Description of experimental and control group interventions according to the template for intervention description and replication (TIDieR)[66]

| | Experimental group | Control group |
|---|---|---|
| Brief name | Progressive resistance training | Non-progressive training |
| Why | To increase muscle strength | To exercise in a way that would not be expected to increase muscle strength |
| What materials | Exercise professional maintains an online logbook to record the content of each session (e.g. exercises performed, weight lifted, number of repetitions and sets) and any adverse events | |
| What procedures | To follow progressive resistance training principles: (1) exercise at sufficient intensity (60-80% of 1 repetition maximum), progressive overload (increase resistance as participant gets stronger) and allow recovery (1-2 minutes between exercise sets and at least one day between sessions) | To commence training with no resistance and progresses to 10% of 1RM (a level insufficient to increase muscle strength). It will remain at this load during the entire program |
| Who provided | An exercise professional (e.g. physiotherapist, exercise physiologist or personal trainer) who has completed an online training module. | |
| How provided | Training will be supervised 1:1 and will usually use pin-loaded weight equipment | |
| Where (setting) | At a community gymnasium local to each participant | |
| When/how much (dose) | 48 sessions each of 60 minutes duration over 24 weeks (total 48 hours) | |
| Tailoring | Resistance will be tailored to the individual (60-80% of their 1 repetition maximum of each exercise). | If necessary, to maintain a participant's interest, skills-based exercise may be incorporated into the program |
| Fidelity checking measures | Adherence to the protocol parameters of attendance, exercise type, intensity and volume, rest periods, and program frequency, duration and progression documented at each session in an online logbook (using REDCap software) | |

*Control group*

Participants allocated to the control group will receive all aspects of the intervention (same setting, supervision, equipment, number of repetitions and sets, duration and frequency). However, participants will exercise at a low intensity, with no progressive overload of muscles. Exercise training will commence using no resistance and will progress to 10% of 1RM (a level insufficient to increase muscle strength) and will remain at this load during the program. This design has been implemented successfully in another trial,[26] allowing attribution of any between group differences to progressive resistance training and not other factors such as therapist attention.

Both groups will be offered two 1-hour planning sessions for participants and their caregivers after the week 25 assessment to discuss continued participation in community-based exercise. Informed by the Health Action Process framework,[27] these sessions will aim to address barriers to community participation and may include information on accessing available resources to support ongoing exercise participation. The content of these sessions will be individualised. The first session will be completed within four weeks and the second session within 12 weeks of program completion.

**Outcome measures**

Outcomes will be assessed at weeks 0 (baseline), 25 (immediately after the intervention; primary endpoint) and 52 by an assessor blind to group allocation (Table 2). Assessments will take place at three sites (Melbourne, Sydney, Brisbane).

*Primary outcome measure*

Muscle strength will be assessed using 1 repetition maximum (1RM) force generation tests for upper limb and lower limb, respectively. These tests establish the amount of weight each participant can lift in a single seated chest press and leg press respectively. Single 1RM chest and leg press tests have high levels of retest reliability ($ICC_{2,1}$ =0.98 chest press; $ICC_{2,1}$=0.81 leg press) and demonstrated no systematic change when measured over 10 weeks in people with PWS.[23]

*Secondary outcome measures*

Muscle mass will be assessed using dual energy x-ray absorptiometry (DXA) whole body scans. DXA provides reliable data on body composition and is widely used in people with PWS.[1] Scans will be completed by a DXA licensed researcher who is blind to group allocation, according to manufacturer's instructions and on equipment calibrated daily. DXA scans will be carried out on the same equipment at each time point for each participant.

Functional strength will be assessed using four tests: sit-to-stand test,[28] weighted box-stacking test,[17] timed stair climb test[29] and 6-minute walk test.[30]

Physical activity will be assessed using Actigraph GT3X+ monitors (triaxial accelerometer) worn by participants on their waistbands for 7 consecutive days during waking hours. Participants will be considered adherent if they wear the monitor for at least 10 hours on at least 4 days including at least one weekend day.

Community participation (attendance or 'being there' and involvement or 'experience') will be assessed using three questionnaires completed by participants, or by parents or caregivers where necessary: the Adolescent Physical Activity Recall[31] questionnaire; the Adolescent Sedentary Activity[32] questionnaire; and, the community module of the Participation and Environment Measure-Children and Youth (PEM-CY).[33]

Health-related quality of life will be assessed using the Child Health Utility (CHU-9D)[34] instrument, a generic preference-based measure completed by the participants, and the parent-report Quality of Life Inventory-Disability (QI-Disability) questionnaire designed specifically for youth with complex disability.[35]

Behaviour will be assessed using the parent-report Developmental Behaviour Checklist,[36] which measures overall behavioural and emotional disturbance and 5 subscale scores (disruptive, self-absorbed, communication disturbance, anxiety, and social-relating disturbance).

Healthcare utilisation will be collected via a health service utilisation questionnaire developed for the trial. The questionnaire will collect data on hospital admissions and community allied health visits. Medicare Australia records will also be retrieved, with participant consent, to determine medical services and pharmaceutical use over one year.

*Other outcomes*

Demographic data on age, sex, medications (including growth hormone), co-morbidities, intellectual disability (parent/caregiver report or formal IQ testing scores if available) and social situation will be recorded at baseline. Anthropometric data on weight, height and waist circumference will be recorded at each assessment using a weighing scale, stadiometer and tape measure respectively, using standardised methods. Diet will be assessed using the online Australian Eating Survey (version 3) which is designed to measure typical food intake and is completed by the participant's parent or caregiver.

*Process evaluation*

Data on intervention fidelity and adverse events will be documented after each exercise session in an online exercise logbook (using REDCap software) by the exercise professional supervising the intervention.

Participant's experiences of exercising at a community gym setting will be explored by collecting qualitative data. Data on acceptability, benefits and social interactions with gym users during training will be documented from semi-structured interviews (conducted either in-person or via telephone or videoconference) with participants, their parent or caregiver and the exercise professional supervising the intervention (Table 2). Interviews will follow a question schedule and will be recorded and transcribed verbatim. Ideas that emerge in early interviews will be explored during later interviews to form a rich, nuanced understanding of the participant's experience. Photographs and short video recordings will also be collected by the exercise professional using an iPod (Apple Inc) provided, and shared with participants prior to the interview, to help stimulate conversations about the participant's experiences.[37, 38] Participants will be asked to talk about aspects of the program important to them and aspects they would consider changing. Brief observations on social interactions with other gym users during training will be documented in the exercise logbook by the supervising exercise professional.

Data about the participant's gym experiences will be complemented by an embedded qualitative observation study, using ethnographic methods, for a subgroup of up to 10 participants living in Victoria. A separate protocol for this embedded study will be reported elsewhere. Briefly, at least three training sessions, one during the initial, middle and final weeks of training, will be observed by a researcher. Overt observation will be used, where participants and exercise professionals are aware of a researcher's presence in the gym. Unstructured observations of the context, the interactions occurring between the person with PWS and other people in the gym and the reactions of others to the presence of the person with PWS will be documented in detail. Scratch notes at the time of observation will be made, from which detailed ethnographic field notes will be recorded that will provide an open-ended description of the exercise session, including events that occurred, reflections about the session, ideas for future observations, and thoughts comparing what was observed with other data reported. Data collection and analysis will occur in parallel, to allow ideas and reflections arising to be explored in subsequent observations.

**Table 2** Outcome measures

| Outcome | Measure | Description | Administration | Week 0 | Week 26 | Week 52 |
|---|---|---|---|---|---|---|
| ***PRIMARY*** | | | | | | |
| Muscle strength | 1RM chest press | Weight a participant can lift in a single seated chest press | Clinician observation | ✓ | ✓ | ✓ |
| | 1RM leg press | Weight a participant can lift in a single leg press | | | | |
| ***SECONDARY*** | | | | | | |
| Muscle mass | DXA whole body scan | Total lean mass, total fat mass, % body fat, regional lean mass, fat distribution | DXA licenced clinician | ✓ | ✓ | ✓ |
| Functional strength | Sit-to-stand | Time taken to stand up and sit down 5 times | Clinician observation | ✓ | ✓ | ✓ |
| | Weighted box stacking | Number of 10 kg boxes participants can lift in 1 min, from floor to a table 75 cm high | Clinician observation | ✓ | ✓ | ✓ |
| | Timed stairs climb | Time taken to ascend and descend a flight of stairs. Fastest time from 2 attempts | Clinician observation | ✓ | ✓ | ✓ |
| | 6-minute walk test | Distance walked in 6 mins over a 25 m course. Continuous encouragement allowed. | Clinician observation | ✓ | ✓ | ✓ |
| Physical activity | Daily total physical activity<br>Daily steps<br>Daily time sedentary | Daily total physical activity<br>Daily steps<br>Daily time spent sedentary | Tri-axial accelerometer worn on the waistband during waking hours for 7 days | ✓ | ✓ | ✓ |
| Community participation | Adolescent physical activity recall questionnaire | Type, duration and frequency of organised and non-organised physical activities done each week | Questionnaire, self-report or proxy-report | ✓ | ✓ | ✓ |
| | Adolescent sedentary activity questionnaire | 12-items, how often participants do sedentary activities on weekdays and weekends | Questionnaire, self-report or proxy-report | ✓ | ✓ | ✓ |
| | Community section of PEM-CY | 10 items, frequency and involvement of a participant in | Questionnaire, self-report or proxy-report | ✓ | ✓ | ✓ |

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|---|---|---|---|---|---|---|
| | | activities | | | | |
| Health-related quality of life | CHU-9D | 9-items, generic measure for young people | Questionnaire, self-report or proxy-report | ✓ | ✓ | ✓ |
| | QI-Disability | 42-items, specific measure for youth with complex disability | Questionnaire, proxy-report | | | |
| Behaviour | Developmental behaviour checklist | 96-items, 5 subscales | Online questionnaire, proxy-report | ✓ | ✓ | ✓ |
| Healthcare utilisation | Health utilisation questionnaire | Hospital admissions and community allied health visits (all cause) | Questionnaire, self-report or proxy-report | ✓ | ✓ | ✓ |
| | Medicare Australia data | Medical services, and pharmaceutical use over 12 months | Report Medicare Australia | | | ✓ |
| Diet | Australian Eating Survey | Food frequency questionnaire designed to measure typical food intake over 3 to 6 months | Online questionnaire, proxy-report | ✓ | ✓ | ✓ |
| ***PROCESS EVALUATION*** | | | | | | |
| Intervention fidelity | Adherence to trial protocol | Attendance, exercise type, intensity and volume, rest periods, and program frequency, duration and progression | Online exercise logbook completed by exercise professional | | ✓ | |
| Safety | Adverse events | Categorised as serious or non-serious, expected or unexpected, related or unrelated to the intervention | Online exercise logbook completed by exercise professional | | ✓ | |
| Gym experience | Participant experience | Exploring the experiences of people with PWS of exercising at a community gym | Semi-structured interviews with participants, their families and exercise professionals | | ✓ | |
| | | | Participant photographs and videos taken during training using iPod | | ✓ | |
| | Participant observation | Ethnographic methods | Researcher observation using ethnographic methods | | ✓ | |

## STATISTICAL ANALYSIS

*Sample size estimation*

Our pilot trial found moderate to large increases (effect sizes 0.78 and 0.92) for upper and lower limb strength after 10 weeks of progressive resistance training in young people with PWS. Assuming an effect size of 0.78, equating to improvement in strength of 15-25%, is clinically significant, two-sided 5% significance level and a power of 80%, a sample size of 27 participants per group (total 54) is necessary. Allowing for a conservative 10% dropout rate (given no dropouts in the pilot trial), we aim to recruit 60 participants.

*Analysis of quantitative outcomes*

Data will be analysed according to intention to treat principles using linear mixed effects models for primary outcomes, with treatment group as a covariate. Modelling will account for variation in baseline values, for within-participant dependence of observations taken over time, and for missing data, allowing some participants to have missing observations at certain time points. Random effects will be used for individuals to account for correlated repeated measures and for site. Visualisation of residuals will be used to look for model assumption errors, and transformations will be used if needed. If outliers are present, a robust linear mixed effects analysis will also be fitted as a sensitivity analysis. If more than 5% of data are missing, a multiple imputation process will be used, providing the assumption data are missing at random is met. A similar approach will be used for analysis of quantitative secondary outcomes. Process evaluation will assess intervention fidelity and will explore causal mechanisms of impact (using mediation analysis[39]) including whether improvements in muscle strength are mediated by changes in muscle mass and other factors associated with variation in outcomes.[40] The CONSORT 2010[41] and the consensus on exercise reporting template (CERT)[42] guidelines will guide reporting.

*Analysis of qualitative outcomes*

The theoretical framework underpinning the qualitative data analysis is interpretive description.[43] Interpretative description seeks to understand experiences in a way that can be meaningfully applied to clinical practice. It was chosen because a focus of this trial is to establish new knowledge of pragmatic strategies that could support successful implementation of exercise programs for people with PWS rather than creating new theory. The Consolidated criteria for Reporting Qualitative research (COREQ) checklist[44] will guide reporting.

Computer software (NVivo; QSR International, Melbourne) will be used to manage the qualitative data analysis of participant interviews. Initial analysis will involve two researchers independently coding transcripts line-by-line. Next, the researchers will meet to review codes and to group emergent codes into categories, subthemes and themes using inductive reasoning. Strategies to ensure credibility, transferability and dependability will include triangulation with quantitative data, exercise logs, and observation data; and using 'rich thick description', whereby verbatim quotations are included to exemplify themes.[45] Member checking will be completed to provide the opportunity for participants to confirm transcripts reflect their thoughts, and to verify interpretation of the data after initial analysis.

*Health economic analysis*

The health economic analysis will evaluate cost-effectiveness from healthcare and societal perspectives, with outcomes based on the primary intermediate clinical outcome (15% difference in leg muscle strength) and the secondary outcome of health-related quality of life

(CHU-9D). The control group are an attention placebo-control; as such the "sham" intervention delivered has no bearing to "usual care". In line with other placebo-control trials, there will be no delivery costs attributed to this group. Program costs associated with the intervention will be attributed to the experimental group only. These will be determined from a register of staff and the time engaged in the supervision of participant training. Labour costs will be attributed to the staff member to determine an intervention cost per experimental group participant. In addition, mean fixed costs associated with training and any other fixed intervention costs will be attributed to experimental group participants. Total costs for each participant will be determined from the intervention costs and cost of self-reported health services and Medicare Services Australia (primary care visits and prescription pharmaceuticals) utilised following completion of the intervention for both groups up to week-52. The incremental cost effectiveness ratio (ICER) around the primary outcome will be calculated as the difference in total program and health service costs between the groups over one year. A cost utility ratio will be calculated based on the secondary outcome measure as the change in total program and health service cost per change in quality adjusted life years saved in the experimental and control groups over one year. One-way sensitivity analyses will investigate robustness of the cost effectiveness ratio to a range of cost and effect estimates. On the cost side, this may include alternative delivery arrangements, including scaling up the intervention, wage rates and program length; on the effect side health-related quality of life and muscle strength. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) will guide reporting.[46]

**Patient and Public Involvement**

This proposal was co-developed in consultation with partner organisations (Prader-Willi Syndrome Association of Australia; Prader-Willi Research Foundation of Australia) and parents of people with PWS. The trial governance structure comprises a project steering committee and a data monitoring committee. The project steering committee will monitor trial implementation and performance, oversee and manage the budget, provide strategic support and specialist advice, identify and manage risks and agreed standard operating procedures. The committee membership will comprise researchers (all chief investigators), clinicians (all associate investigators) and at least two consumer representatives from the PWS community. The steering committee meets bi-monthly by videoconference and will meet face-to-face as required. The data monitoring committee will meet at least once a year to monitor safety and data quality and will review any adverse events that occur. This committee will comprise a chair from the research team and two independent expert clinicians from participating sites.

**ETHICS AND DISSEMINATION**

Ethical approval was granted by Royal Children's Hospital, Melbourne through the National Mutual Acceptance initiative as participants will be recruited throughout Australia. Research governance approval was obtained from five sites (Royal Children's Hospital, Melbourne; Austin Hospital, Melbourne; Royal Prince Alfred Hospital, Sydney; Queensland Children's Hospital, Brisbane; Princess Alexandra Hospital, Brisbane). Ethics approval was registered with relevant universities. Any modifications to the protocol will be submitted for ethics approval and noted on the trial registration.

Young adults with PWS (18 and over) will provide their own written informed consent to participate where they provide their own consent in usual practice. For adults who do not normally provide their own consent, their legal guardian will provide written informed

consent on their behalf, consistent with the relevant Act covering medical decision making in the jurisdiction.[47] In this case, the adult with PWS is also invited to provide their own written consent. For adolescents with PWS (13 to 17 years), written informed consent will be obtained from their parents or guardians. Adolescents with PWS are also invited to provide their own written consent based on their parents' recommendation for whether this is appropriate. Allocation is concealed at the time of consent and consent will be obtained by the trial coordinator. Separate consent will also be sought to access participant data from the Medicare Benefits Scheme and Pharmaceutical Benefits Scheme.

Participant confidentiality is strictly held in trust by the investigators, research staff, and the sponsoring institution. All identifiable participant data, including clinical data, will be held in strict confidence and will not be released to any unauthorised third party without written permission of the participant, except as necessary for monitoring by the ethics committee or regulatory agencies.

Given the dearth of literature to support the design and delivery of exercise programs for people with cognitive disability and behavioural challenges, a knowledge translation plan guided by the Practical Robust Implementation and Sustainability Model[48] to support adoption and implementation of strategies and processes for people with PWS is incorporated within this trial. We aim to meet the needs of people with PWS, their families and the health and recreation sectors by (1) planning for sustainability through the development of free resources to assist implementation of exercise programs for people with PWS by exercise professionals, community exercise venues, and other local health agencies; (2) sharing best practice by gathering exemplars of implementation; (3) facilitating access to exercise opportunities by working with parents, caregivers and others (e.g. residential care facility staff) on how community exercise programs articulate with available disability funding and mapping implementation costs; (4) training those who work with people with PWS through professional development seminars; and, (5) disseminating outcomes broadly to people with PWS and their families (e.g. newsletters, blogs, social media, public talks) and health professionals (e.g. publications, presentations). The contribution of the participants with PWS will be directly acknowledged. Consistent with Australian National Health and Medical Research Council policies, de-identified data from the trial will be made available through OPAL, La Trobe University's Institutional Repository or through online supplemental data files accompanying publication of findings.

This randomised controlled trial will determine the efficacy and cost-effectiveness of community-based progressive resistance training for people with PWS. By incorporating embedded health economic evaluation and qualitative analysis of exercise participation experiences, it will provide robust clinical and health economic data to inform policy and practice.

**Authors' contributions:** NS led the research team in the conception, design and coordination of this trial, acquisition of funding and the drafting and critical revision of the manuscript. KB, LR, TM, CB, NT contributed as chief investigators to the trial design, acquisition of funding, in ongoing monitoring of trial progress, and critically reviewed the manuscript. AS contributed substantially as the trial coordinator and the revision of the manuscript. LP contributed to the trial design (sample size estimation and data analysis plan), acquisition of funding, is involved in the ongoing monitoring of trial progress and critically reviewed this manuscript. JW contributed to the study design (economic evaluation component), acquisition of funding, project steering committees and critical revision of this manuscript. CS contributed as a PhD student (qualitative data collection and analysis) and to revision of the manuscript. VC, JF, DL, GL, ZM, JP, SB contributed as associate investigators (clinical expertise) contributing to trial design, acquisition of funding and critical revision of this manuscript. SB contributed substantially as a consumer representative to the development of trial resources and processes and to the revision of the manuscript. All authors read and approved the final manuscript.

**Competing interests statement:** None declared.

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**Data sharing statement:** Individual participant data for published primary and secondary quantitative outcome measures will be made available via open access (university library repository) following the publication of the main trial outcomes.

**Trial status:** Enrolment for the trial began in February 2020 and is still in progress. Data collection will continue until the target sample size is reached, expected June 2022.

**Ethics approval**: Ethics approval was obtained from Royal Children's Hospital, Melbourne HREC/50874/RCHM-2019 under the National Mutual Acceptance initiative. Ethics approval has been registered with La Trobe University, the University of Melbourne and Deakin University.

**Trial personnel:** The PRESTO trial research team comprises:
*Chief investigators*
Prof Nora Shields, La Trobe University
Prof Kim Bennell, The University of Melbourne
Prof Nicholas F. Taylor, La Trobe University and Eastern Health
Doctor Lauren Rice, The University of Sydney
A/Prof Tania Markovic, The University of Sydney
Prof Christine Bigby, La Trobe University
A/Prof Jennifer J. Watts, Deakin University
A/Prof Luke Prendergast, La Trobe University

*Associate investigators*
Doctor Viral Chikani, Princess Alexandra Hospital, Brisbane
Doctor David Levitt, Queensland Children's Hospital, Brisbane
Doctor Janet Franklin, Royal Prince Alfred Hospital
Ms Georgina Loughnan, Royal Prince Alfred Hospital
Doctor Zoe McCallum, Royal Children's Hospital, Melbourne
Prof Joe Proietto, Austin Health, Melbourne
Rosalyn DeVries, consumer representative, Prader Willi Research Foundation
Susan Blair, consumer representative, Prader Willi Research Foundation

*Project staff*
Alesha Southby (trial coordinator)
Cara Schofield (research student)

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**FIGURE LEGEND**

**Figure 1** Trial Design

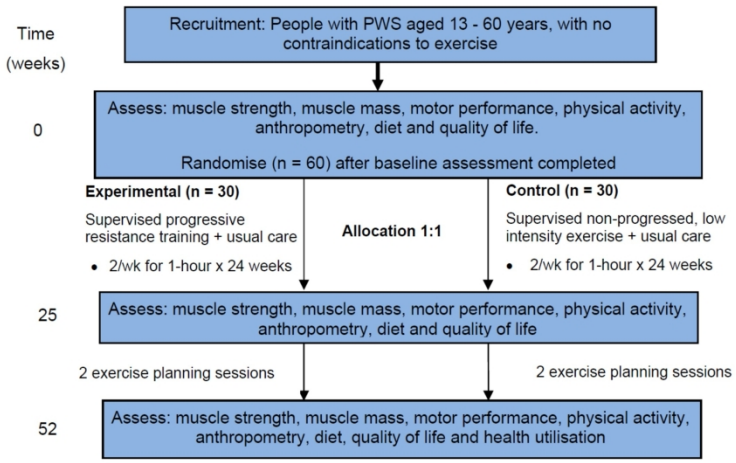


Figure 1 Trial design

209x297mm (300 x 300 DPI)

# Trial Review

COVID-19 studies are our top priority.

For new and updated trial submissions, we are processing trials as quickly as possible and appreciate your patience. We recommend submitting your trial for registration at the same time as ethics submission.

VIEW TRIAL AT REGISTRATION VIEW HISTORY

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been endorsed by the ANZCTR. Before participating in a study, talk to your health care provider and refer to this information for consumers

< BACK

## Trial registered on ANZCTR

| | |
|---|---|
| **Registration number** | ACTRN12620000416998 |
| **Ethics application status** | Approved |
| **Date submitted** | 12/03/2020 |
| **Date registered** | 27/03/2020 |
| **Date last updated** | 21/10/2021 |
| **Date data sharing statement initially provided** | 27/03/2020 |
| **Type of registration** | Prospectively registered |

### Titles & IDs

| | |
|---|---|
| **Public title** | Improving muscle strength in young people with Prader-Willi syndrome: a phase II randomised trial |
| **Scientific title** | The effect of exercise on muscle strength in young people with Prader-Willi syndrome: a phase II randomised trial |
| **Secondary ID [1]** | None |
| **Universal Trial Number (UTN)** | |
| **Trial acronym** | PRESTO |
| **Linked study record** | |

### Health condition

**Health condition(s) or problem(s) studied:**

Prader-Willi syndrome

| **Condition category** | **Condition code** |
|---|---|
| Human Genetics and Inherited Disorders | Other human genetics and inherited disorders |

### Intervention/exposure

| | |
|---|---|
| **Study type** | Interventional |
| **Description of intervention(s) / exposure** | Participants will be randomised to receive one of two exercises programs.<br>Intervention group participants will complete an exercise program, supervised 1:1 by an exercise professional.<br>Participants will exercise twice a week for 24 weeks (48 sessions in total). Each exercise session will last |

| | |
|---|---|
| | approximately 60 minutes.<br>All exercise sessions will take place in a community gym local to the participant.<br>The exercise program will be supervised by an exercise professional (usually a physiotherapist, exercise physiologist or personal trainer). Exercise professionals will be invited to participate based on their location and typical practice (e.g. working in paediatrics, neurological, or musculoskeletal areas). They will receive a training manual that includes details about the trial protocol, specialist advice on Prader-Willi syndrome, how to facilitate exercise in people with Prader-Willi syndrome, communication strategies, and behaviour management.<br>The exercise professional will complete an exercise log (either in hard copy or online) on behalf of the participant to document the exercises completed and any adverse events that occur.<br>Participants will also receive 2 planning sessions of 1-hour duration following the intervention period with a facilitator to encourage their ongoing participation in community exercise. These sessions will be conducted by an exercise professional either in person or via videoconference. The content of these sessions will be individualised and will aim to address barriers to taking part in ongoing community exercise. These sessions will take place approximately 1 month and 3 months after the end of the intervention. |
| **Intervention code [1]** | Rehabilitation |
| **Comparator / control treatment** | Control group participants will also complete an exercise program, supervised 1:1 by an exercise professional.<br>Participants will exercise twice a week for 24 weeks (48 sessions in total). Each exercise session will last approximately 60 mins,<br>All exercise sessions will take place in a community gym local to the participant.<br>The exercise program will be supervised by an exercise professional (usually a physiotherapist, exercise physiologist or personal trainer).<br>Exercise professionals will be invited to participate based on their location and typical practice (e.g. working in paediatrics, neurological, or musculoskeletal areas). They will receive a training manual that includes details about the trial protocol, specialist advice on Prader-Willi syndrome, how to facilitate exercise in people with Prader-Willi syndrome, communication strategies, and behaviour management,<br>The exercise professional will complete an exercise log (either in hard copy of online) on behalf of the participant to document the exercises completed and any adverse events that occur.<br>Participants will also received 2 planning sessions of 1-hour duration following the intervention period with a facilitator to encourage their ongoing participation in community exercise. These sessions will be conducted by an exercise professional either in person or via videoconference. The content of these sessions will be individualised and will aim to address barriers to taking part in ongoing community exercise. These sessions will take place approximately 1 month and 3 months after the end of the intervention. |
| **Control group** | Active |

## Outcomes

| | |
|---|---|
| **Primary outcome [1]** | Muscle strength- of the arms and legs will be assessed using 1 repetition maximum (1RM) force generation tests. Composite measures of arm (chest press) and leg (leg press) strength will establish the amount of weight each participant can lift once. |
| ***Timepoint [1]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [1]** | Lean muscle mass will be assessed using a dual energy x-ray absorptiometry (DXA) whole body scan for total lean (muscle) mass and regional lean mass. DXA scans will be carried out on the same equipment at each time point for each participant at each site. |
| ***Timepoint [1]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [2]** | Sit-to-stand test: measures how long it takes to stand up and sit down 5 times |
| ***Timepoint [2]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [3]** | Weighted box-stacking test: measures how many boxes weighing 10kg can be stacked in one minute |
| ***Timepoint [3]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [4]** | Timed stair climb test: measures how long it takes to go up and down a standard flight of stairs |
| ***Timepoint [4]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [5]** | 6-minute walk test: measures distance walked by the participant in 6 minutes |
| ***Timepoint [5]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [6]** | Physical activity levels (accelerometry): Actigraph GT3X+ accelerometers will be used to measure total physical activity, total sedentary time and the number of steps participants take during waking hours over 7 consecutive days. |
| ***Timepoint [6]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [7]** | Community participation (attendance): will be measured using the Adolescent Physical Activity Recall, the Adolescent Sedentary Activity, and the community section of the Participation and Environment Measure-Children and Youth questionnaires. These questionnaires measure what sports and other physical activities the participant does, how often and for how long and will be completed by participants and/or their family member or residential caregivers where necessary. |
| ***Timepoint [7]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [8]** | Community participation (involvement): will be measured using the community section of the Participation |

| | |
|---|---|
| | and Environment Measure-Children and Youth questionnaire. This questionnaire measures how involved participants feel in 10 activities and will be completed by participants and/or their family member or residential caregivers where necessary. |
| ***Timepoint [8]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [9]** | Health related quality of life: will be measured using the 9-item Child Health Utility (CHU-9D) instrument and the Quality of Life Inventory-Disability questionnaire. The CHU-9D will be completed by participants and/or their family members or residential caregivers where necessary. The Quality of Life Inventory-Disability questionnaire will be completed by family members or caregivers. |
| ***Timepoint [9]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [10]** | Healthcare utilisation: will be assessed via a health service utilisation questionnaire developed for the trial and completed by participants and/or their family members or residential caregivers where necessary. The questionnaire will collect data on hospital admissions and community allied health visits. |
| ***Timepoint [10]*** | Week O (baseline, week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [11]** | Adverse events: will be categorised as serious or non-serious, expected or unexpected, and related or unrelated to the trial will be documented in the participant's exercise logbook completed by the health professional (usually a physiotherapist) supervising the intervention. Examples of possible adverse events are delayed onset muscle soreness, increased anxiety resulting in skin picking or a temper outburst (behavioural features of Prader-Willi syndrome) and food stealing. |
| ***Timepoint [11]*** | During intervention phase of the trial (compiled at week 25, immediately post intervention) |
| **Secondary outcome [12]** | Diet: will be documented by parents and carers (not participants) using the online version of the Australian Eating Survey |
| ***Timepoint [12]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [13]** | Gym experience: qualitative data about the participants' experience of exercise will be collected from both groups (intervention and control). Data on acceptability, benefits and social interactions with gym users during training will be documented from semi-structured interviews with participants and their families. Photographs and video diaries will also be collected by participants using an iPod touch given to them on loan by the research team at trial commencement. Data on social interactions with other gym users will be documented in the participant's exercise log during training by the health professional delivering the intervention. Data collection will be supplemented by observation (using ethnographic methods) for a subgroup of participants (n=10 participants), where 3 training sessions (one session during initial weeks, middle weeks and final weeks of training) will be observed. |
| ***Timepoint [13]*** | During intervention phase of the trial (compiled at week 25, immediately post intervention) |
| **Secondary outcome [14]** | Behaviour will be measured using the Developmental Behaviour Checklist questionnaire. The Developmental Behaviour Checklist -Parent version (DBC-P) will be completed by family members or residential caregivers of adolescents (aged 13-17 years) and the Developmental Behaviour Checklist -Adult version (DBC-A) will be completed by family members or residential caregivers of adults (aged 18 years and over). |
| ***Timepoint [14]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [15]** | Medicare Australia records will be retrieved with participant consent to determine medical services and pharmaceutical use over 12 months. |
| ***Timepoint [15]*** | Week 52 (6-months post-intervention) |

## Eligibility

| | |
|---|---|
| **Key inclusion criteria** | Each participant must meet all of the following criteria to be enrolled in this trial:<br>• Have genetically confirmed Prader-Willi syndrome,<br>• Aged between 13 and 60 years (inclusive) at the time of randomisation,<br>• Able to follow simple verbal instructions in English,<br>• Medical clearance from their general practitioners or physician certifying they can participate (where considered necessary based on answers to the pre-exercise screening questionnaire PAR-Q+),<br>• Provide a signed and dated informed consent form or has a legally acceptable representative capable of understanding the informed consent document and providing consent on the participant's behalf. |
| **Minimum age** | 13 Years |
| **Maximum age** | 60 Years |
| **Gender** | Both males and females |
| **Can healthy volunteers participate?** | No |
| **Key exclusion criteria** | People meeting any of the following criteria will be excluded from the trial:<br>• Has participated in progressive resistance training in the 3 months prior to randomisation<br>• Has a concurrent physical (e.g. severe arthritis), psychological (e.g. severe psychosis) or behavioural issue (e.g. violent behaviour) that might affect their ability to participate in a 24-week exercise program.<br>• Inability or unwillingness of participant or legally acceptable representative to give written informed consent. |

## Study design

| | |
|---|---|
| **Purpose of the study** | Treatment |
| **Allocation to intervention** | Randomised controlled trial |
| **Procedure for enrolling a subject and allocating the treatment (allocation concealment procedures)** | |
| **Methods used to generate the sequence in which subjects will be randomised (sequence generation)** | |
| **Masking / blinding** | Blinded (masking used) |
| **Who is / are masked / blinded?** | The people receiving the treatment/s<br><br>The people assessing the outcomes<br>The people analysing the results/data |
| **Intervention assignment** | Parallel |
| **Other design features** | |
| **Phase** | Not Applicable |
| **Type of endpoint(s)** | |
| **Statistical methods / analysis** | |

## Recruitment

**Recruitment status** Recruiting

**Date of first participant enrolment**

**Anticipated** 3/04/2020 **Actual** 24/02/2021

**Date of last participant enrolment**

**Anticipated** **Actual**

**Date of last data collection**

**Anticipated** **Actual**

**Sample size**

**Target** 60 **Accrual to date** 24 **Final**

**Recruitment in Australia**

| | |
|---|---|
| **Recruitment state(s)** | NSW,QLD,VIC |
| **Recruitment hospital [1]** | The Royal Childrens Hospital - Parkville |
| **Recruitment hospital [2]** | Royal Prince Alfred Hospital - Camperdown |
| **Recruitment hospital [3]** | Princess Alexandra Hospital - Woolloongabba |
| **Recruitment hospital [4]** | Queensland Children's Hospital - South Brisbane |
| **Recruitment hospital [5]** | Austin Health - Austin Hospital - Heidelberg |
| **Recruitment postcode(s) [1]** | 3052 - Parkville |
| **Recruitment postcode(s) [2]** | 2050 - Camperdown |
| **Recruitment postcode(s) [3]** | 4102 - Woolloongabba |
| **Recruitment postcode(s) [4]** | 4101 - South Brisbane |
| **Recruitment postcode(s) [5]** | 3084 - Heidelberg |

## Funding & Sponsors

| | |
|---|---|
| **Funding source category [1]** | Government body |
| **Name [1]** | Medical Research Future Fund |
| **Address [1]** | Department of Health<br>GPO Box 9848<br>Canberra ACT 2601<br>Australia |
| **Country [1]** | Australia |
| **Primary sponsor type** | University |
| **Name** | La Trobe University |

| | |
|---|---|
| **Address** | Kingsbury Drive,<br>Bundoora,<br>VIC 3086 |
| **Country** | Australia |
| **Secondary sponsor category [1]** | None |
| **Name [1]** | |
| **Address [1]** | |
| **Country [1]** | |

## Ethics approval

| | |
|---|---|
| **Ethics application status** | Approved |
| **Ethics committee name [1]** | The Royal Children's Hospital Melbourne Human Research Ethics Committee |
| **Ethics committee address [1]** | 50 Flemington Rd,<br>Parkville<br>VIC 3052 |
| **Ethics committee country [1]** | Australia |
| **Date submitted for ethics approval [1]** | |
| **Approval date [1]** | 18/04/2019 |
| **Ethics approval number [1]** | 2019.048 |

## Summary

| | |
|---|---|
| **Brief summary** | We will investigate if exercise is effective in increasing muscle strength in people with Prader-Willi syndrome (PWS). We will conduct a phase II, multi-site, double-blind, randomised controlled trial with 6-month follow-up. Sixty participants with PWS aged 13 to 60 years will be randomised to receive one of two exercise programs. Participants will exercise twice a week for 24 weeks at their local gym supervised by an exercise health professional (usually a physiotherapist). We will measure muscle strength, muscle mass, functional strength, physical activity, community participation, and health-related quality of life at baseline (week 0), after the intervention (week 25) and 6 months later (week 52): We will recruit participants through PWS advocacy groups, specialist PWS clinics, and PWS registries and clinical databases. |
| **Trial website** | |
| **Trial related presentations / publications** | |
| **Public notes** | |

## Contacts

### Principal investigator

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|---|---|
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### Contact person for public queries

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## Data sharing statement

| | |
|---|---|
| **Will individual participant data (IPD) for this trial be available (including data dictionaries)?** | Yes |
| **What data in particular will be shared?** | Individual participant data for published primary and secondary quantitative outcome measures. |
| **When will data be available (start and end dates)?** | Following the publication of the main trial outcomes (circa 2024), no end date. |
| **Available to whom?** | Data will be open access. |
| **Available for what types of analyses?** | Data will be available for any purpose including meta-analyses. |
| **How or where can data be obtained?** | Data will be deposited in the La Trobe University library repository. |
| **What supporting documents are/will be available?** | Study protocol<br>Ethical approval |

## How or where can supporting documents be obtained?

| | |
|---|---|
| Type [1] | Ethical approval |
| Citation [1] | |
| Link [1] | |
| Email [1] | |
| Other [1] | |
| Attachment [1] | /Steps11and12/377484-(Uploaded-08-07-2019-12-31-15)-Study-related document.pdf |
| Type [2] | Study protocol |
| Citation [2] | |
| Link [2] | |
| Email [2] | |
| Other [2] | We aim to publish a study protocol in an open access journal. |
| Attachment [2] | |

## Summary results

No Results

< BACK

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

| Section/item | ItemNo | Description | Manuscript location |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | p. 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | p.3 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | p.1, 3-14; Figure 1, Table 1 and 2 |
| Protocol version | 3 | Date and version identifier | Appendix 1 |
| Funding | 4 | Sources and types of financial, material, and other support | p.15 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | p.1; 15-16 |
| | 5b | Name and contact information for the trial sponsor | n/a |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | p.15 |
| | 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) | p.13 |
| **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 | p.4-5 |
| | 6b | Explanation for choice of comparators | n/a |
| Objectives | 7 | Specific objectives or hypotheses | p.5 |

| | | | |
|---|---|---|---|
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | p.5 |
| **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 | p.5-6 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | p.5 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | p.6-8 |
| | 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) | p.6 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | p.6 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | p.6 |
| 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 | p.8-9 Table 2 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Figure 1 |
| 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 | p.12 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | p.6 |

**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 | p.5 |
| 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 | p.5 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | p.5 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | p.6 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | n/a |

**Methods: Data collection, management, and analysis**

| | | | |
|---|---|---|---|
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | p.8-9, Table 2 |
| | 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 | p.12 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | p. 12-14 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | p.12-13 |

| | | | |
|---|---|---|---|
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | p.12-13 |
| | 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) | p.12 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | p.13 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | P 9, Table 2 |
| 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 | p.13-14 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | p. 13 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | p.13-14 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | p.14 |

| | | | |
|---|---|---|---|
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | p.15 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | p.15 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | n/a |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | p.14 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | n/a |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | p.15 |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Not included for submission but can be provided upon request |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a |

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

BMJ Open

# Progressive resistance training in young people with Prader-Willi syndrome: protocol for a randomised trial (PRESTO)



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| Secondary Subject Heading: | Rehabilitation medicine |
| Keywords: | Developmental neurology & neurodisability < PAEDIATRICS, Clinical trials < THERAPEUTICS, PUBLIC HEALTH, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT |
| | |

**TITLE:** Progressive resistance training in young people with Prader-Willi syndrome: protocol for a randomised trial (PRESTO)

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**KEYWORDS:** Prader-Willi Syndrome, Exercise, strength training, disability, resistance, physical activity, young adult, community

## ABSTRACT

**Introduction:** Preliminary evidence suggests progressive resistance training may be beneficial for people with Prader-Willi Syndrome (PWS), a rare genetic condition that results in muscle weakness and low muscle tone.

**Aims**: To establish if community-based progressive resistance training is effective in improving the muscle strength of people with PWS; to determine cost-effectiveness; and, to complete a process evaluation assessing intervention fidelity, exploring mechanisms of impact, understanding participant experiences and identifying contextual factors affecting implementation.

**Methods and analysis:** A multisite, randomised controlled trial will be completed. Sixty participants with PWS will be randomised to receive either progressive resistance training (experimental) or non-progressive exercise (placebo-control). Participants will be aged 13 to 60 years, be able to follow simple instructions in English, and have no contraindications to performing progressive resistance training. The experimental group will complete progressive resistance training twice weekly for 24 weeks supervised by an exercise professional at a community gym. The control group will receive all aspects of the intervention except progressive overload. Outcomes will be assessed at week 25 (primary endpoint) and week 52 by a blinded assessor. The primary outcome is muscle strength assessed using one repetition maximum for upper limb and lower limb. Secondary outcomes are muscle mass, functional strength, physical activity, community participation, health-related quality of life and behaviour. Health economic analysis will evaluate cost-effectiveness. Process evaluation will assess safety and intervention fidelity, investigate mechanism of impact, explore participant experiences and identify contextual factors affecting implementation. Data collection commenced in February 2020 and will conclude in September 2023.

**Ethics and dissemination**: Ethical approval was obtained from The Royal Children's Hospital Human Research Ethics Committee (HREC/50874/RCHM-2019) under the National Mutual Acceptance initiative. Research governance approvals were obtained from five clinical sites. Results will be disseminated through published manuscripts, conference presentations, public seminars and practical resources for stakeholder groups.

**Trial registration** Australian and New Zealand Clinical Trial Registry (ACTRN12620000416998).


**Strengths and limitations of this study:**

- Multisite randomised controlled trial recruiting participants from across Australia to investigate the effectiveness of progressive resistance training for people with Prader-Willi Syndrome on muscle strength (primary outcome), muscle mass, functional strength, physical activity, behaviour and participation.
- Inclusion of an embedded health economic analysis will evaluate cost-effectiveness of progressive resistance training from healthcare and societal perspectives, with outcomes based on muscle strength (primary outcome) and health-related quality of life (secondary outcome).

- An embedded process evaluation will assess intervention safety and fidelity, mechanism of impact, participant experiences and contextual factors affecting implementation.
- Participants and assessors will be blinded to group allocation, however it is not possible to blind exercise professionals. Quantitative data analysis will be blinded.

## INTRODUCTION

Prader-Willi syndrome (PWS) is a rare condition with extensive musculoskeletal sequelae resulting from a genetic abnormality on chromosome 15 at q11–13.[1] Approximately 400,000 people live with PWS worldwide.[2] In combination with hyperphagia (uncontrolled urge to eat), intellectual disability,[3] emotional outbursts[4] and anxiety,[5] PWS can result in premature death[6] due to extreme obesity.[7, 8] Limited treatments exist and health care costs are high; estimated in 2016 to be €60k per individual per annum.[9],[10],[11]

The musculoskeletal features of PWS include abnormal growth and body composition.[12] People with PWS have very low lean body mass, muscle weakness and hypotonia. Their muscle mass is 25 to 40% lower and their muscle strength approximately 70% lower than those without PWS. This has detrimental effects on physical functioning, causing severe delay in childhood motor development and persistent mobility problems in adulthood.[12] Approximately 90% of people with PWS require assistance with activities of daily living.[13] For people with PWS, muscle weakness, hypotonia and poor motor proficiency can reduce the desire to be active,[14] leading to a cycle of sedentary behaviour, deteriorating muscle function, obesity, greater metabolic risk, social isolation, lower quality of life,[15] and early mortality.[3] Increasing muscle strength in a program sufficiently long to establish an exercise routine and behaviour change has the potential to have clinical impact for people with PWS by improving their mobility, making it easier to perform activities of daily living and physical activity.

The musculoskeletal features of PWS also adversely impact metabolic function. Having very low muscle mass limits the ability to balance increased energy intake due to hyperphagia, making weight control difficult. Medications to increase muscle mass are either ineffective[16] or expensive. Usual care in PWS comprises aerobic exercise and a strictly controlling diet. However, aerobic exercise targets cardiovascular fitness rather than increases in muscle strength or muscle mass and so does not directly address altered body composition. Aerobic exercise also requires coordination, concentration and time commitment, which can affect adherence and make it difficult for those with mobility problems, complex behavioural issues and intellectual disability.

Muscle strength and muscle mass are increased by progressive resistance training (strength training) in the general[17] and other disability populations,[18] when implemented with sufficient intensity and progression of load.[19] No trials have investigated the effect of progressive resistance training in people with PWS, so it is unclear if it will have the intended effect given the genetic basis to their muscle weakness (their muscles may not adapt to training) and their complex behavioural issues could be a substantial threat to regular exercise adherence. Progressive resistance training requires high loads to be lifted for a low number of repetitions before muscular fatigue, with load progression as the person gets stronger. Preliminary evidence from three small studies in children[20, 21] and adults with PWS,[22] demonstrate proof-of-principle that muscle strengthening exercise can increase strength[22] and muscle mass,[20],[21] leading to improvements in walking[22] and physical activity.[20] However, in these studies the training was usually not progressed; was home-based requiring parental supervision; and, the research designs lacked rigour due to no randomisation, control groups, or blinded assessment. A recent randomised feasibility trial ($n$=16) of a 10-week program supervised by a physiotherapist successfully implemented progressive resistance training with excellent attendance (92%) and adherence (82%) and few minor adverse events.[23] Estimates of effect were moderate to large in favour of progressive resistance

training compared to a waitlist control group. A qualitative study conducted alongside the trial found the supervising physiotherapists perceived progressive resistance training achieved important clinical outcomes related to fostering independence and confidence in the participants with PWS. Thus, increasing muscle strength in young people with PWS could mean less need for assistance with activities of daily living (reducing carer burden and costs) and improved ability to participate in physical activity, improving health and reducing obesity-related comorbidity. Establishing an exercise routine may also provide the impetus to ongoing participation in regular physical activity.

Therefore, our primary aim is to establish if 6-months community-based progressive resistance training is effective in improving the arm and leg muscle strength of people with PWS. Our secondary aims are to:
(i) determine if progressive resistance training leads to changes in muscle mass, functional strength physical activity, community participation, health-related quality of life and behaviour;
(ii) determine if progressive resistance training is cost-effective in people with PWS; and
(iii) complete a process evaluation that assesses intervention safety and fidelity, explores mechanisms of impact, understands participant experiences, explores contextual factors affecting implementation and identifies pragmatic strategies for successful implementation of progressive resistance training in those with intellectual disabilities and behavioural challenges.

## METHODS AND ANALYSIS

### Trial design

A multisite, parallel-group randomised controlled trial (RCT) with follow-up at one year, and embedded health economic and process evaluations, will be conducted. Participants with PWS will be randomly allocated to either the experimental group (progressive resistance training) or a placebo-control group (non-progressive exercise) (Fig 1). Randomisation will be in a 1:1 ratio with stratification by trial location (VIC, NSW or QLD) and minimisation (by age, sex, type of PWS and receipt of growth hormone therapy) with a random component of 80%. Randomisation will occur after eligibility has been determined, the participant has consented, and a baseline assessment completed. Randomisation will be coordinated by Griffith University Randomisation Service, Queensland, Australia. The trial has been registered prospectively, including updates, with the Australian and New Zealand Clinical Trial Registry (online supplemental appendix 1).

### Participants

To be eligible for inclusion, participants must meet the following criteria:
(1) have genetically confirmed PWS, and live in Australia;
(2) aged between 13 and 60 years; andf
(3) able to follow verbal instructions in English.

People will be excluded if they:
(1) have participated in progressive resistance training in the 3 months prior to randomisation; or,
(2) have a concurrent physical or mental health condition (e.g., severe arthritis, severe psychosis, physically aggressive behaviour) affecting their ability to participate in community-based exercise.

**Recruitment**

Participants will be recruited through four sources:

(i) Population registries or clinical databases (e.g. Victorian PWS register; Global PWS Registry; and the Australian National PWS database). Custodians of these databases will send a copy of the trial advertisement to potential participants.

(ii) Specialist PWS clinics in Melbourne, Sydney, and Brisbane. Potential participants will be informed of the trial by their treating doctor or therapist.

(iii) PWS advocacy groups based in Australia will send a copy of the flyer advertising the trial to their members.

(iv) Parent and carer networks (including social media groups): research team members who are parents of people with PWS will disseminate information about the trial to their personal networks and through parent and carer forums.

Prospective participants or their caregiver will complete a screening process by telephone with a research team member to assess their eligibility for the trial, including the completion of a pre-exercise screening questionnaire (PAR-Q+).[24] If any concerns related to suitability to take part are identified, they will be asked to obtain medical clearance prior to enrolment (e.g. unexplained symptoms such as chest pain or shortness of breath at rest).

**Intervention**

All participants will continue to receive their usual health care, which will be documented. All participants will complete an exercise program and will be blinded to their group allocation.

*Experimental group*

Participants allocated to the experimental group will complete progressive resistance training twice a week for 24 weeks at a community gymnasium (Table 1). The program, designed according to American College of Sports Medicine guidelines,[17] will comprise 6 exercises: 3 for the upper limbs (e.g. lat pull down) and 3 for the lower limbs (e.g. seated calf raise). Exercises will be performed on pin-loaded weight machines, as these are safer for novices than free weights. Exercises can be modified to suit the availability of equipment at a particular gym. Participants will perform up to 3 sets of 12 repetitions of each exercise until fatigue (intensity of 60-80% of 1 repetition maximum, 1RM). A 2-minute rest will be taken between each set to allow recovery, and resistance will be increased when 3 sets of 12 repetitions of an exercise can be completed. Each training session will last approximately one hour.

Participants will be supervised 1:1 by an exercise professional (Table 1). Supervision will ensure participants exercise at the correct intensity, provide physical and motivational support, and limit participant access to food.[25] The supervising professional will document the program in an online exercise logbook (including exercises performed, weight lifted, number of repetitions and sets). Supervisors will be invited to participate based on their location. They will receive training on the trial protocol, specialist advice on PWS, facilitating exercise in people with PWS, communication strategies, and proactively managing PWS behaviours such as emotional outbursts. The supervisor training will be delivered via a university online learning site and a printed training manual.

Table 1. Description of experimental and control group interventions according to the template for intervention description and replication (TIDieR)[26]

| | Experimental group | Control group |
|---|---|---|
| Brief name | Progressive resistance training | Non-progressive training |
| Why | To increase muscle strength | To exercise in a way that would not be expected to increase muscle strength |
| What materials | Exercise professional maintains an online logbook to record the content of each session (e.g. exercises performed, weight lifted, number of repetitions and sets) and any adverse events | |
| What procedures | To follow progressive resistance training principles: (1) exercise at sufficient intensity (60-80% of 1 repetition maximum), progressive overload (increase resistance as participant gets stronger) and allow recovery (1-2 minutes between exercise sets and at least one day between sessions) | To commence training with no resistance and progresses to 10% of 1RM (a level insufficient to increase muscle strength). It will remain at this load during the entire program |
| Who provided | An exercise professional (e.g. physiotherapist, exercise physiologist or personal trainer) who has completed an online training module. | |
| How provided | Training will be supervised 1:1 and will usually use pin-loaded weight equipment | |
| Where (setting) | At a community gymnasium local to each participant | |
| When/how much (dose) | 48 sessions each of 60 minutes duration over 24 weeks (total 48 hours) | |
| Tailoring | Resistance will be tailored to the individual (60-80% of their 1 repetition maximum of each exercise). | If necessary, to maintain a participant's interest, skills-based exercise may be incorporated into the program |
| Fidelity checking measures | Adherence to the protocol parameters of attendance, exercise type, intensity and volume, rest periods, and program frequency, duration and progression documented at each session in an online logbook (using REDCap software) | |

*Control group*

Participants allocated to the control group will receive all aspects of the intervention (same setting, supervision, equipment, number of repetitions and sets, duration and frequency). However, participants will exercise at a low intensity, with no progressive overload of muscles. Exercise training will commence using no resistance and will progress to 10% of 1RM (a level insufficient to increase muscle strength) and will remain at this load during the program. This design has been implemented successfully in another trial,[27] allowing attribution of any between group differences to progressive resistance training and not other factors such as therapist attention.

Both groups will be offered two 1-hour planning sessions for participants and their caregivers after the week 25 assessment to discuss continued participation in community-based exercise. Informed by the Health Action Process framework,[28] these sessions will aim to address barriers to community participation and may include information on accessing available resources to support ongoing exercise participation. The content of these sessions will be individualised. The first session will be completed within four weeks and the second session within 12 weeks of program completion.

**Outcome measures**

Outcomes will be assessed at weeks 0 (baseline), 25 (immediately after the intervention; primary endpoint) and 52 by an assessor blind to group allocation (Table 2). Assessments will take place at three sites (Melbourne, Sydney, Brisbane).

*Primary outcome measure*

Muscle strength will be assessed using 1 repetition maximum (1RM) force generation tests for upper limb and lower limb, respectively. These tests establish the amount of weight each participant can lift in a single seated chest press and leg press respectively. Single 1RM chest and leg press tests have high levels of retest reliability ($ICC_{2,1}$ =0.98 chest press; $ICC_{2,1}$=0.81 leg press) and demonstrated no systematic change when measured over 10 weeks in people with PWS.[23]

*Secondary outcome measures*

Muscle mass will be assessed using dual energy x-ray absorptiometry (DXA) whole body scans. DXA provides reliable data on body composition and is widely used in people with PWS.[1] Scans will be completed by a DXA licensed researcher who is blind to group allocation, according to manufacturer's instructions and on equipment calibrated daily. DXA scans will be carried out on the same equipment at each time point for each participant.

Functional strength will be assessed using four tests: sit-to-stand test,[29] weighted box-stacking test,[17] timed stair climb test[30] and 6-minute walk test.[31]

Physical activity will be assessed using Actigraph GT3X+ monitors (triaxial accelerometer) worn by participants on their waistbands for 7 consecutive days during waking hours. Participants will be considered adherent if they wear the monitor for at least 10 hours on at least 4 days including at least one weekend day.

Community participation (attendance or 'being there' and involvement or 'experience') will be assessed using three questionnaires completed by participants, or by parents or caregivers where necessary: the Adolescent Physical Activity Recall[32] questionnaire; the Adolescent Sedentary Activity[33] questionnaire; and, the community module of the Participation and Environment Measure-Children and Youth (PEM-CY).[34]

Health-related quality of life will be assessed using the Child Health Utility (CHU-9D)[35] instrument, a generic preference-based measure completed by the participants, and the parent-report Quality of Life Inventory-Disability (QI-Disability) questionnaire designed specifically for youth with complex disability.[36]

Behaviour will be assessed using the parent-report Developmental Behaviour Checklist,[37] which measures overall behavioural and emotional disturbance and 5 subscale scores (disruptive, self-absorbed, communication disturbance, anxiety, and social-relating disturbance).

Healthcare utilisation will be collected via a health service utilisation questionnaire developed for the trial. The questionnaire will collect data on hospital admissions and community allied health visits. Medicare Australia records will also be retrieved, with participant consent, to determine medical services and pharmaceutical use over one year.

*Other outcomes*

Demographic data on age, sex, medications (including growth hormone), co-morbidities, intellectual disability (parent/caregiver report or formal IQ testing scores if available) and social situation will be recorded at baseline. Anthropometric data on weight, height and waist circumference will be recorded at each assessment using a weighing scale, stadiometer and tape measure respectively, using standardised methods. Diet will be assessed using the online Australian Eating Survey (version 3) which is designed to measure typical food intake and is completed by the participant's parent or caregiver.

*Process evaluation*

Data on intervention fidelity and adverse events will be documented after each exercise session in an online exercise logbook (using REDCap software) by the exercise professional supervising the intervention.

Participant's experiences of exercising at a community gym setting will be explored by collecting qualitative data. Data on acceptability, benefits and social interactions with gym users during training will be documented from semi-structured interviews (conducted either in-person or via telephone or videoconference) with participants, their parent or caregiver and the exercise professional supervising the intervention (Table 2). Interviews will follow a question schedule and will be recorded and transcribed verbatim. Ideas that emerge in early interviews will be explored during later interviews to form a rich, nuanced understanding of the participant's experience. Photographs and short video recordings will also be collected by the exercise professional using an iPod (Apple Inc) provided, and shared with participants prior to the interview, to help stimulate conversations about the participant's experiences.[38, 39] Participants will be asked to talk about aspects of the program important to them and aspects they would consider changing. Brief observations on social interactions with other gym users during training will be documented in the exercise logbook by the supervising exercise professional.

Data about the participant's gym experiences will be complemented by an embedded qualitative observation study, using ethnographic methods, for a subgroup of up to 10 participants living in Victoria. A separate protocol for this embedded study will be reported elsewhere. Briefly, at least three training sessions, one during the initial, middle and final weeks of training, will be observed by a researcher. Overt observation will be used, where participants and exercise professionals are aware of a researcher's presence in the gym. Unstructured observations of the context, the interactions occurring between the person with PWS and other people in the gym and the reactions of others to the presence of the person with PWS will be documented in detail. Scratch notes at the time of observation will be made, from which detailed ethnographic field notes will be recorded that will provide an open-ended description of the exercise session, including events that occurred, reflections about the session, ideas for future observations, and thoughts comparing what was observed with other data reported. Data collection and analysis will occur in parallel, to allow ideas and reflections arising to be explored in subsequent observations.

**Table 2** Outcome measures

| Outcome | Measure | Description | Administration | Week 0 | Week 25 | Week 52 |
|---|---|---|---|---|---|---|
| ***PRIMARY*** | | | | | | |
| Muscle strength | 1RM chest press | Weight a participant can lift in a single seated chest press | Clinician observation | ✓ | ✓ | ✓ |
| | 1RM leg press | Weight a participant can lift in a single leg press | | | | |
| ***SECONDARY*** | | | | | | |
| Muscle mass | DXA whole body scan | Total lean mass, total fat mass, % body fat, regional lean mass, fat distribution | DXA licenced clinician | ✓ | ✓ | ✓ |
| Functional strength | Sit-to-stand | Time taken to stand up and sit down 5 times | Clinician observation | ✓ | ✓ | ✓ |
| | Weighted box stacking | Number of 10 kg boxes participants can lift in 1 min, from floor to a table 75 cm high | Clinician observation | ✓ | ✓ | ✓ |
| | Timed stairs climb | Time taken to ascend and descend a flight of stairs. Fastest time from 2 attempts | Clinician observation | ✓ | ✓ | ✓ |
| | 6-minute walk test | Distance walked in 6 mins over a 25 m course. Continuous encouragement allowed. | Clinician observation | ✓ | ✓ | ✓ |
| Physical activity | Daily total physical activity<br>Daily steps<br>Daily time sedentary | Daily total physical activity<br>Daily steps<br>Daily time spent sedentary | Tri-axial accelerometer worn on the waistband during waking hours for 7 days | ✓ | ✓ | ✓ |
| Community participation | Adolescent physical activity recall questionnaire | Type, duration and frequency of organised and non-organised physical activities done each week | Questionnaire, self-report or proxy-report | ✓ | ✓ | ✓ |
| | Adolescent sedentary activity questionnaire | 12-items, how often participants do sedentary activities on weekdays and weekends | Questionnaire, self-report or proxy-report | ✓ | ✓ | ✓ |
| | Community section of PEM-CY | 10 items, frequency and involvement of a participant in | Questionnaire, self-report or proxy-report | ✓ | ✓ | ✓ |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | activities | | | | |
| Health-related quality of life | CHU-9D | 9-items, generic measure for young people | Questionnaire, self-report or proxy-report | ✓ | ✓ | ✓ |
| | QI-Disability | 42-items, specific measure for youth with complex disability | Questionnaire, proxy-report | | | |
| Behaviour | Developmental behaviour checklist | 96-items, 5 subscales | Online questionnaire, proxy-report | ✓ | ✓ | ✓ |
| Healthcare utilisation | Health utilisation questionnaire | Hospital admissions and community allied health visits (all cause) | Questionnaire, self-report or proxy-report | ✓ | ✓ | ✓ |
| | Medicare Australia data | Medical services, and pharmaceutical use over 12 months | Report Medicare Australia | | | ✓ |
| Diet | Australian Eating Survey | Food frequency questionnaire designed to measure typical food intake over 3 to 6 months | Online questionnaire, proxy-report | ✓ | ✓ | ✓ |
| ***PROCESS EVALUATION*** | | | | | | |
| Intervention fidelity | Adherence to trial protocol | Attendance, exercise type, intensity and volume, rest periods, and program frequency, duration and progression | Online exercise logbook completed by exercise professional | | ✓ | |
| Safety | Adverse events | Categorised as serious or non-serious, expected or unexpected, related or unrelated to the intervention | Online exercise logbook completed by exercise professional | | ✓ | |
| Gym experience | Participant experience | Exploring the experiences of people with PWS of exercising at a community gym | Semi-structured interviews with participants, their families and exercise professionals | | ✓ | |
| | | | Participant photographs and videos taken during training using iPod | | ✓ | |
| | Participant observation | Ethnographic methods | Researcher observation using ethnographic methods | | ✓ | |

## STATISTICAL ANALYSIS

*Sample size estimation*

Our pilot trial found moderate to large increases (effect sizes 0.78 and 0.92) for upper and lower limb strength after 10 weeks of progressive resistance training in young people with PWS. Assuming an effect size of 0.78, equating to improvement in strength of 15-25%, is clinically significant, two-sided 5% significance level and a power of 80%, a sample size of 27 participants per group (total 54) is necessary. Allowing for a conservative 10% dropout rate (given no dropouts in the pilot trial), we aim to recruit 60 participants.

*Analysis of quantitative outcomes*

Data will be analysed according to intention to treat principles using linear mixed effects models for primary outcomes, with treatment group as a covariate. Modelling will account for variation in baseline values, for within-participant dependence of observations taken over time, and for missing data, allowing some participants to have missing observations at certain time points. Random effects will be used for individuals to account for correlated repeated measures and for site. Visualisation of residuals will be used to look for model assumption errors, and transformations will be used if needed. If outliers are present, a robust linear mixed effects analysis will also be fitted as a sensitivity analysis. If more than 5% of data are missing, a multiple imputation process will be used, providing the assumption data are missing at random is met and where covariates related to missingness will be used to generate the imputed data. If multiple imputation is required, the results will be used as a sensitivity analysis to compare with the main analysis to check for any potential biases related to missingness. A similar approach will be used for analysis of quantitative secondary outcomes. Process evaluation will assess intervention fidelity (including confirming progression in resistance during training over 24 weeks and if ceiling effects are observed) and will explore causal mechanisms of impact (using mediation analysis[40]) including whether improvements in muscle strength are mediated by changes in muscle mass and other factors associated with variation in outcomes.[41] The CONSORT 2010[42] and the consensus on exercise reporting template (CERT)[43] guidelines will guide reporting.

*Analysis of qualitative outcomes*

The theoretical framework underpinning the qualitative data analysis is interpretive description.[44] Interpretative description seeks to understand experiences in a way that can be meaningfully applied to clinical practice. It was chosen because a focus of this trial is to establish new knowledge of pragmatic strategies that could support successful implementation of exercise programs for people with PWS rather than creating new theory. The Consolidated criteria for Reporting Qualitative research (COREQ) checklist[45] will guide reporting.

Computer software (NVivo; QSR International, Melbourne) will be used to manage the qualitative data analysis of participant interviews. Initial analysis will involve two researchers independently coding transcripts line-by-line. Next, the researchers will meet to review codes and to group emergent codes into categories, subthemes and themes using inductive reasoning. Strategies to ensure credibility, transferability and dependability will include triangulation with quantitative data, exercise logs, and observation data; and using 'rich thick description', whereby verbatim quotations are included to exemplify themes.[46] Member checking will be completed to provide the opportunity for participants to confirm transcripts reflect their thoughts, and to verify interpretation of the data after initial analysis.

*Health economic analysis*

The health economic analysis will evaluate cost-effectiveness from healthcare and societal perspectives, with outcomes based on the primary intermediate clinical outcome (15% difference in leg muscle strength) and the secondary outcome of health-related quality of life (CHU-9D). The control group are an attention placebo-control; as such the "sham" intervention delivered has no bearing to "usual care". In line with other placebo-control trials, there will be no delivery costs attributed to this group. Program costs associated with the intervention will be attributed to the experimental group only. These will be determined from a register of staff and the time engaged in the supervision of participant training. Labour costs will be attributed to the staff member to determine an intervention cost per experimental group participant. In addition, mean fixed costs associated with training and any other fixed intervention costs will be attributed to experimental group participants. Total costs for each participant will be determined from the intervention costs and cost of self-reported health services and Medicare Services Australia (primary care visits and prescription pharmaceuticals) utilised following completion of the intervention for both groups up to week-52. The incremental cost effectiveness ratio (ICER) around the primary outcome will be calculated as the difference in total program and health service costs between the groups over one year. A cost utility ratio will be calculated based on the secondary outcome measure as the change in total program and health service cost per change in quality adjusted life years saved in the experimental and control groups over one year. One-way sensitivity analyses will investigate robustness of the cost effectiveness ratio to a range of cost and effect estimates. On the cost side, this may include alternative delivery arrangements, including scaling up the intervention, wage rates and program length; on the effect side health-related quality of life and muscle strength. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) will guide reporting.[47]

**Patient and Public Involvement**

This proposal was co-developed in consultation with partner organisations (Prader-Willi Syndrome Association of Australia; Prader-Willi Research Foundation of Australia) and parents of people with PWS. The trial governance structure comprises a project steering committee and a data monitoring committee. The project steering committee will monitor trial implementation and performance, oversee and manage the budget, provide strategic support and specialist advice, identify and manage risks and agreed standard operating procedures. The committee membership will comprise researchers (all chief investigators), clinicians (all associate investigators) and at least two consumer representatives from the PWS community. The steering committee meets bi-monthly by videoconference and will meet face-to-face as required. The data monitoring committee will meet at least once a year to monitor safety and data quality and will review any adverse events that occur. This committee will comprise a chair from the research team and two expert clinicians from participating sites.

**ETHICS AND DISSEMINATION**

Ethical approval was granted by Royal Children's Hospital, Melbourne through the National Mutual Acceptance initiative as participants will be recruited throughout Australia. Research governance approval was obtained from five sites (Royal Children's Hospital, Melbourne; Austin Hospital, Melbourne; Royal Prince Alfred Hospital, Sydney; Queensland Children's Hospital, Brisbane; Princess Alexandra Hospital, Brisbane). Ethics approval was registered with relevant universities. Any modifications to the protocol will be submitted for ethics approval and noted on the trial registration.

Young adults with PWS (18 and over) will provide their own written informed consent to participate where they provide their own consent in usual practice. For adults who do not normally provide their own consent, their legal guardian will provide written informed consent on their behalf, consistent with the relevant Act covering medical decision making in the jurisdiction.[48] In this case, the adult with PWS is also invited to provide their own written consent (online supplemental appendix 2). For adolescents with PWS (13 to 17 years), written informed consent will be obtained from their parents or guardians. Adolescents with PWS are also invited to provide their own written consent based on their parents' recommendation for whether this is appropriate. Allocation is concealed at the time of consent and consent will be obtained by the trial coordinator. Separate consent will also be sought to access participant data from the Medicare Benefits Scheme and Pharmaceutical Benefits Scheme.

Participant confidentiality is strictly held in trust by the investigators, research staff, and the sponsoring institution. All identifiable participant data, including clinical data, will be held in strict confidence and will not be released to any unauthorised third party without written permission of the participant, except as necessary for monitoring by the ethics committee or regulatory agencies.

Our procedure for adverse events is for these to be recorded during the intervention period until resolution or stabilisation, regardless of their relationship to the intervention. The exercise professional supervising the training is responsible for recording in the participant's exercise logbook the date, actions taken. and outcome of the adverse event; and for the Principal Investigator to subsequently record the expectedness, severity, seriousness and association to the intervention, based on temporal relationship and clinical judgment. The exercise professional will report all serious adverse events within 24 hours to the Principal Investigator, who will then submit a report to the approving Human Research Ethics Committee and to the relevant research governance offices without undue delay and no later than 15 calendar days. The report will clarify the impact of the event on participant safety, trial conduct and trial documentation. La Trobe University has clinical trial insurance in place in case of serious adverse events occurring during this trial.

Given the dearth of literature to support the design and delivery of exercise programs for people with cognitive disability and behavioural challenges, a knowledge translation plan guided by the Practical Robust Implementation and Sustainability Model[49] to support adoption and implementation of strategies and processes for people with PWS is incorporated within this trial. We aim to meet the needs of people with PWS, their families and the health and recreation sectors by (1) planning for sustainability through the development of free resources to assist implementation of exercise programs for people with PWS by exercise professionals, community exercise venues, and other local health agencies; (2) sharing best practice by gathering exemplars of implementation; (3) facilitating access to exercise opportunities by working with parents, caregivers and others (e.g. residential care facility staff) on how community exercise programs articulate with available disability funding and mapping implementation costs; (4) training those who work with people with PWS through professional development seminars; and, (5) disseminating outcomes broadly to people with PWS and their families (e.g. newsletters, blogs, social media, public talks) and health professionals (e.g. publications, presentations). The contribution of the participants with PWS will be directly acknowledged. Consistent with Australian National Health and Medical

Research Council policies, de-identified data from the trial will be made available through OPAL, La Trobe University's Institutional Repository or through online supplemental data files accompanying publication of findings.

## DISCUSSION

The outcomes of this trial have the potential to improve the clinical management of people with PWS. Strength training is not part of usual clinical care for people with PWS and if found to be effective, it would be a good exercise choice as the required skills can usually be mastered by people with intellectual disabilities.[50] Muscle weakness, low muscle tone and poor motor proficiency can reduce the desire of people with PWS to be physically active. This in turn reduces their participation in exercise,[14] leading to a cycle of sedentary behaviour, deteriorating muscle function, obesity, greater metabolic risk, social isolation, lower quality of life,[15] and early mortality.[51] Therefore, facilitating adequate muscle strength could help break the cycle of sedentary behaviour and encouraging healthy lifestyle behaviours.

This trial is designed to help meet the needs of people with PWS, their families and the broader health community. Exercise program availability with one-on-one support emerged as a major theme in a survey of the needs of 105 families with a child or youth with PWS.[13] This trial will provide high-level evidence of how to effectively implement exercise in local community-settings for people with PWS. Their complex behavioural issues are a substantial threat to exercise adherence, and so it is important to determine what pragmatic strategies support community-based exercise participation for people with PWS. Integrated knowledge translation plans are a vital part of all randomised controlled trials to address the disconnect between research and practice.[52] There is limited literature available to support the design and delivery of exercise programs for people with intellectual disability. Our knowledge translation plan includes broad dissemination of our outputs to health and community groups to address this implementation knowledge gap. Future research could investigate the potential for similar active recreation initiatives to reduce health inequality and poor health outcomes by increasing inclusion in community exercise for people with complex disabilities such as PWS.

There is a dearth of clinical trials involving adults with intellectual disability.[53] A strength of this research is that when completed it will be the largest efficacy trial of an exercise intervention for people with PWS. By incorporating a health economic evaluation, it will also provide high-level evidence of whether strength training is a cost-effective intervention for people with PWS. This is important as people with PWS and their families need high-quality evidence to support them to make evidence-informed healthcare decisions. The combination of robust clinical and economic data will also provide high-quality evidence to inform health and disability policy decisions. A limitation of this trial is the paucity of outcome measures to assess participation and health-related quality of life outcomes for adolescents and adults with PWS. While the measures selected were designed for adolescents up to the age of 17 years, these measures have been implemented with young adults with disability up to the age of 30 years in a previous trial.[54]

This randomised controlled trial will determine the efficacy and cost-effectiveness of community-based progressive resistance training for people with PWS. By incorporating embedded health economic evaluation and qualitative analysis of exercise participation experiences, it will provide robust clinical and health economic data to inform policy and practice.

**Authors' contributions:** NS led the research team in the conception, design and coordination of this trial, acquisition of funding and the drafting and critical revision of the manuscript. KB, LR, TM, CB, NT contributed as chief investigators to the trial design, acquisition of funding, in ongoing monitoring of trial progress, and critically reviewed the manuscript. AS contributed substantially as the trial coordinator and the revision of the manuscript. LP contributed to the trial design (sample size estimation and data analysis plan), acquisition of funding, is involved in the ongoing monitoring of trial progress and critically reviewed this manuscript. JW contributed to the study design (economic evaluation component), acquisition of funding, project steering committees and critical revision of this manuscript. CS contributed as a PhD student (qualitative data collection and analysis) and to revision of the manuscript. VC, JF, DL, GL, ZM, JP, SB contributed as associate investigators (clinical expertise) contributing to trial design, acquisition of funding and critical revision of this manuscript. SB contributed substantially as a consumer representative to the development of trial resources and processes and to the revision of the manuscript. All authors read and approved the final manuscript.

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**Data sharing statement:** Individual participant data for published primary and secondary quantitative outcome measures will be made available via open access (university library repository) following the publication of the main trial outcomes.

**Trial status:** Enrolment for the trial began in February 2020 and the final participant was randomised in September 2022. Data collection will continue until September 2023.

**Ethics approval**: Ethics approval was obtained from Royal Children's Hospital, Melbourne HREC/50874/RCHM-2019 under the National Mutual Acceptance initiative. Ethics approval has been registered with La Trobe University, the University of Melbourne and Deakin University.

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## FIGURE LEGEND

**Figure 1** Trial Design

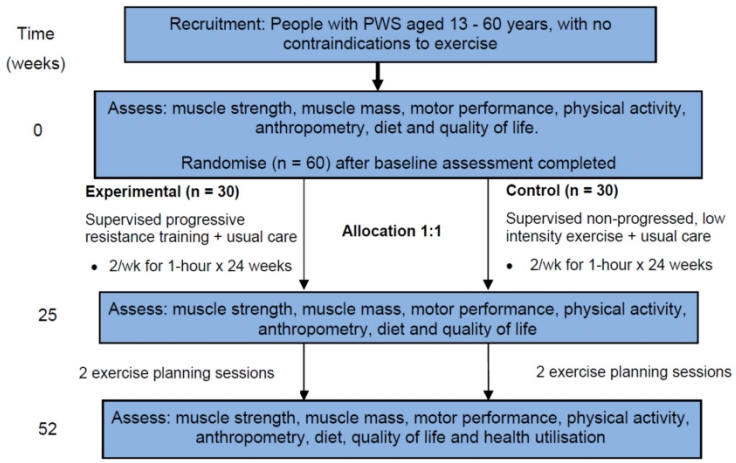


Figure 1 Trial design

209x297mm (300 x 300 DPI)

# Trial Review

COVID-19 studies are our top priority.

For new and updated trial submissions, we are processing trials as quickly as possible and appreciate your patience. We recommend submitting your trial for registration at the same time as ethics submission.

VIEW TRIAL AT REGISTRATION VIEW HISTORY

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been endorsed by the ANZCTR. Before participating in a study, talk to your health care provider and refer to this information for consumers

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## Trial registered on ANZCTR

| | |
|---|---|
| **Registration number** | ACTRN12620000416998 |
| **Ethics application status** | Approved |
| **Date submitted** | 12/03/2020 |
| **Date registered** | 27/03/2020 |
| **Date last updated** | 21/10/2021 |
| **Date data sharing statement initially provided** | 27/03/2020 |
| **Type of registration** | Prospectively registered |

### Titles & IDs

| | |
|---|---|
| **Public title** | Improving muscle strength in young people with Prader-Willi syndrome: a phase II randomised trial |
| **Scientific title** | The effect of exercise on muscle strength in young people with Prader-Willi syndrome: a phase II randomised trial |
| **Secondary ID [1]** | None |
| **Universal Trial Number (UTN)** | |
| **Trial acronym** | PRESTO |
| **Linked study record** | |

### Health condition

**Health condition(s) or problem(s) studied:**

Prader-Willi syndrome

| **Condition category** | **Condition code** |
|---|---|
| Human Genetics and Inherited Disorders | Other human genetics and inherited disorders |

### Intervention/exposure

| | |
|---|---|
| **Study type** | Interventional |
| **Description of intervention(s) / exposure** | Participants will be randomised to receive one of two exercises programs.<br>Intervention group participants will complete an exercise program, supervised 1:1 by an exercise professional.<br>Participants will exercise twice a week for 24 weeks (48 sessions in total). Each exercise session will last |

| | |
|---|---|
| | approximately 60 minutes.<br>All exercise sessions will take place in a community gym local to the participant.<br>The exercise program will be supervised by an exercise professional (usually a physiotherapist, exercise physiologist or personal trainer). Exercise professionals will be invited to participate based on their location and typical practice (e.g. working in paediatrics, neurological, or musculoskeletal areas). They will receive a training manual that includes details about the trial protocol, specialist advice on Prader-Willi syndrome, how to facilitate exercise in people with Prader-Willi syndrome, communication strategies, and behaviour management.<br>The exercise professional will complete an exercise log (either in hard copy or online) on behalf of the participant to document the exercises completed and any adverse events that occur.<br>Participants will also receive 2 planning sessions of 1-hour duration following the intervention period with a facilitator to encourage their ongoing participation in community exercise. These sessions will be conducted by an exercise professional either in person or via videoconference. The content of these sessions will be individualised and will aim to address barriers to taking part in ongoing community exercise. These sessions will take place approximately 1 month and 3 months after the end of the intervention. |
| **Intervention code [1]** | Rehabilitation |
| **Comparator / control treatment** | Control group participants will also complete an exercise program, supervised 1:1 by an exercise professional.<br>Participants will exercise twice a week for 24 weeks (48 sessions in total). Each exercise session will last approximately 60 mins,<br>All exercise sessions will take place in a community gym local to the participant.<br>The exercise program will be supervised by an exercise professional (usually a physiotherapist, exercise physiologist or personal trainer).<br>Exercise professionals will be invited to participate based on their location and typical practice (e.g. working in paediatrics, neurological, or musculoskeletal areas). They will receive a training manual that includes details about the trial protocol, specialist advice on Prader-Willi syndrome, how to facilitate exercise in people with Prader-Willi syndrome, communication strategies, and behaviour management,<br>The exercise professional will complete an exercise log (either in hard copy of online) on behalf of the participant to document the exercises completed and any adverse events that occur.<br>Participants will also received 2 planning sessions of 1-hour duration following the intervention period with a facilitator to encourage their ongoing participation in community exercise. These sessions will be conducted by an exercise professional either in person or via videoconference. The content of these sessions will be individualised and will aim to address barriers to taking part in ongoing community exercise. These sessions will take place approximately 1 month and 3 months after the end of the intervention. |
| **Control group** | Active |

## Outcomes

| | |
|---|---|
| **Primary outcome [1]** | Muscle strength- of the arms and legs will be assessed using 1 repetition maximum (1RM) force generation tests. Composite measures of arm (chest press) and leg (leg press) strength will establish the amount of weight each participant can lift once. |
| ***Timepoint [1]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [1]** | Lean muscle mass will be assessed using a dual energy x-ray absorptiometry (DXA) whole body scan for total lean (muscle) mass and regional lean mass. DXA scans will be carried out on the same equipment at each time point for each participant at each site. |
| ***Timepoint [1]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [2]** | Sit-to-stand test: measures how long it takes to stand up and sit down 5 times |
| ***Timepoint [2]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [3]** | Weighted box-stacking test: measures how many boxes weighing 10kg can be stacked in one minute |
| ***Timepoint [3]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [4]** | Timed stair climb test: measures how long it takes to go up and down a standard flight of stairs |
| ***Timepoint [4]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [5]** | 6-minute walk test: measures distance walked by the participant in 6 minutes |
| ***Timepoint [5]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [6]** | Physical activity levels (accelerometry): Actigraph GT3X+ accelerometers will be used to measure total physical activity, total sedentary time and the number of steps participants take during waking hours over 7 consecutive days. |
| ***Timepoint [6]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [7]** | Community participation (attendance): will be measured using the Adolescent Physical Activity Recall, the Adolescent Sedentary Activity, and the community section of the Participation and Environment Measure-Children and Youth questionnaires. These questionnaires measure what sports and other physical activities the participant does, how often and for how long and will be completed by participants and/or their family member or residential caregivers where necessary. |
| ***Timepoint [7]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [8]** | Community participation (involvement): will be measured using the community section of the Participation |

| | |
|---|---|
| | and Environment Measure-Children and Youth questionnaire. This questionnaire measures how involved participants feel in 10 activities and will be completed by participants and/or their family member or residential caregivers where necessary. |
| ***Timepoint [8]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [9]** | Health related quality of life: will be measured using the 9-item Child Health Utility (CHU-9D) instrument and the Quality of Life Inventory-Disability questionnaire. The CHU-9D will be completed by participants and/or their family members or residential caregivers where necessary. The Quality of Life Inventory-Disability questionnaire will be completed by family members or caregivers. |
| ***Timepoint [9]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [10]** | Healthcare utilisation: will be assessed via a health service utilisation questionnaire developed for the trial and completed by participants and/or their family members or residential caregivers where necessary. The questionnaire will collect data on hospital admissions and community allied health visits. |
| ***Timepoint [10]*** | Week O (baseline, week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [11]** | Adverse events: will be categorised as serious or non-serious, expected or unexpected, and related or unrelated to the trial will be documented in the participant's exercise logbook completed by the health professional (usually a physiotherapist) supervising the intervention. Examples of possible adverse events are delayed onset muscle soreness, increased anxiety resulting in skin picking or a temper outburst (behavioural features of Prader-Willi syndrome) and food stealing. |
| ***Timepoint [11]*** | During intervention phase of the trial (compiled at week 25, immediately post intervention) |
| **Secondary outcome [12]** | Diet: will be documented by parents and carers (not participants) using the online version of the Australian Eating Survey |
| ***Timepoint [12]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [13]** | Gym experience: qualitative data about the participants' experience of exercise will be collected from both groups (intervention and control). Data on acceptability, benefits and social interactions with gym users during training will be documented from semi-structured interviews with participants and their families. Photographs and video diaries will also be collected by participants using an iPod touch given to them on loan by the research team at trial commencement. Data on social interactions with other gym users will be documented in the participant's exercise log during training by the health professional delivering the intervention. Data collection will be supplemented by observation (using ethnographic methods) for a subgroup of participants (n=10 participants), where 3 training sessions (one session during initial weeks, middle weeks and final weeks of training) will be observed. |
| ***Timepoint [13]*** | During intervention phase of the trial (compiled at week 25, immediately post intervention) |
| **Secondary outcome [14]** | Behaviour will be measured using the Developmental Behaviour Checklist questionnaire. The Developmental Behaviour Checklist -Parent version (DBC-P) will be completed by family members or residential caregivers of adolescents (aged 13-17 years) and the Developmental Behaviour Checklist -Adult version (DBC-A) will be completed by family members or residential caregivers of adults (aged 18 years and over). |
| ***Timepoint [14]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [15]** | Medicare Australia records will be retrieved with participant consent to determine medical services and pharmaceutical use over 12 months. |
| ***Timepoint [15]*** | Week 52 (6-months post-intervention) |

## Eligibility

| | |
|---|---|
| **Key inclusion criteria** | Each participant must meet all of the following criteria to be enrolled in this trial:<br>• Have genetically confirmed Prader-Willi syndrome,<br>• Aged between 13 and 60 years (inclusive) at the time of randomisation,<br>• Able to follow simple verbal instructions in English,<br>• Medical clearance from their general practitioners or physician certifying they can participate (where considered necessary based on answers to the pre-exercise screening questionnaire PAR-Q+),<br>• Provide a signed and dated informed consent form or has a legally acceptable representative capable of understanding the informed consent document and providing consent on the participant's behalf. |
| **Minimum age** | 13 Years |
| **Maximum age** | 60 Years |
| **Gender** | Both males and females |
| **Can healthy volunteers participate?** | No |
| **Key exclusion criteria** | People meeting any of the following criteria will be excluded from the trial:<br>• Has participated in progressive resistance training in the 3 months prior to randomisation<br>• Has a concurrent physical (e.g. severe arthritis), psychological (e.g. severe psychosis) or behavioural issue (e.g. violent behaviour) that might affect their ability to participate in a 24-week exercise program.<br>• Inability or unwillingness of participant or legally acceptable representative to give written informed consent. |

## Study design

| | |
|---|---|
| **Purpose of the study** | Treatment |
| **Allocation to intervention** | Randomised controlled trial |
| **Procedure for enrolling a subject and allocating the treatment (allocation concealment procedures)** | |
| **Methods used to generate the sequence in which subjects will be randomised (sequence generation)** | |
| **Masking / blinding** | Blinded (masking used) |
| **Who is / are masked / blinded?** | The people receiving the treatment/s<br><br>The people assessing the outcomes<br>The people analysing the results/data |
| **Intervention assignment** | Parallel |
| **Other design features** | |
| **Phase** | Not Applicable |
| **Type of endpoint(s)** | |
| **Statistical methods / analysis** | |

## Recruitment

| | |
|---|---|
| **Recruitment status** | Recruiting |

**Date of first participant enrolment**

| | | | |
|---|---|---|---|
| **Anticipated** | 3/04/2020 | **Actual** | 24/02/2021 |

**Date of last participant enrolment**

| | | | |
|---|---|---|---|
| **Anticipated** | | **Actual** | |

**Date of last data collection**

| | | | |
|---|---|---|---|
| **Anticipated** | | **Actual** | |

**Sample size**

| | | | | | |
|---|---|---|---|---|---|
| **Target** | 60 | **Accrual to date** | 24 | **Final** | |

**Recruitment in Australia**

| | |
|---|---|
| **Recruitment state(s)** | NSW,QLD,VIC |
| **Recruitment hospital [1]** | The Royal Childrens Hospital - Parkville |
| **Recruitment hospital [2]** | Royal Prince Alfred Hospital - Camperdown |
| **Recruitment hospital [3]** | Princess Alexandra Hospital - Woolloongabba |
| **Recruitment hospital [4]** | Queensland Children's Hospital - South Brisbane |
| **Recruitment hospital [5]** | Austin Health - Austin Hospital - Heidelberg |
| **Recruitment postcode(s) [1]** | 3052 - Parkville |
| **Recruitment postcode(s) [2]** | 2050 - Camperdown |
| **Recruitment postcode(s) [3]** | 4102 - Woolloongabba |
| **Recruitment postcode(s) [4]** | 4101 - South Brisbane |
| **Recruitment postcode(s) [5]** | 3084 - Heidelberg |

## Funding & Sponsors

| | |
|---|---|
| **Funding source category [1]** | Government body |
| **Name [1]** | Medical Research Future Fund |
| **Address [1]** | Department of Health<br>GPO Box 9848<br>Canberra ACT 2601<br>Australia |
| **Country [1]** | Australia |
| **Primary sponsor type** | University |
| **Name** | La Trobe University |

| | |
|---|---|
| **Address** | Kingsbury Drive,<br>Bundoora,<br>VIC 3086 |
| **Country** | Australia |
| **Secondary sponsor category [1]** | None |
| **Name [1]** | |
| **Address [1]** | |
| **Country [1]** | |

## Ethics approval

| | |
|---|---|
| **Ethics application status** | Approved |
| **Ethics committee name [1]** | The Royal Children's Hospital Melbourne Human Research Ethics Committee |
| **Ethics committee address [1]** | 50 Flemington Rd,<br>Parkville<br>VIC 3052 |
| **Ethics committee country [1]** | Australia |
| **Date submitted for ethics approval [1]** | |
| **Approval date [1]** | 18/04/2019 |
| **Ethics approval number [1]** | 2019.048 |

## Summary

| | |
|---|---|
| **Brief summary** | We will investigate if exercise is effective in increasing muscle strength in people with Prader-Willi syndrome (PWS). We will conduct a phase II, multi-site, double-blind, randomised controlled trial with 6-month follow-up. Sixty participants with PWS aged 13 to 60 years will be randomised to receive one of two exercise programs. Participants will exercise twice a week for 24 weeks at their local gym supervised by an exercise health professional (usually a physiotherapist). We will measure muscle strength, muscle mass, functional strength, physical activity, community participation, and health-related quality of life at baseline (week 0), after the intervention (week 25) and 6 months later (week 52): We will recruit participants through PWS advocacy groups, specialist PWS clinics, and PWS registries and clinical databases. |
| **Trial website** | |
| **Trial related presentations / publications** | |
| **Public notes** | |

## Contacts

### Principal investigator

| | |
|---|---|
| **Name** | Prof Nora Shields |
| **Address** | Department of Physiotherapy, Podiatry, Prosthetics and Orthotics,<br>La Trobe University,<br>VIC 3086 |
| **Country** | Australia |
| **Phone** | +61 3 9479 5852 |
| Fax | |
| **Email** | n.shields@latrobe.edu.au |

### Contact person for public queries

| | |
|---|---|
| **Name** | Prof Nora Shields |
| **Address** | Department of Physiotherapy, Podiatry, Prosthetics and Orthotics,<br>La Trobe University,<br>VIC 3086 |
| **Country** | Australia |
| **Phone** | +61 3 9479 5852 |
| Fax | |
| **Email** | n.shields@latrobe.edu.au |

### Contact person for scientific queries

| | |
|---|---|
| **Name** | Prof Nora Shields |

| | |
|---|---|
| **Address** | Department of Physiotherapy, Podiatry, Prosthetics and Orthotics,<br>La Trobe University,<br>VIC 3086 |
| **Country** | Australia |
| **Phone** | +61 3 9479 5852 |
| Fax | |
| **Email** | n.shields@latrobe.edu.au |


## Data sharing statement

| | |
|---|---|
| **Will individual participant data (IPD) for this trial be available (including data dictionaries)?** | Yes |
| **What data in particular will be shared?** | Individual participant data for published primary and secondary quantitative outcome measures. |
| **When will data be available (start and end dates)?** | Following the publication of the main trial outcomes (circa 2024), no end date. |
| **Available to whom?** | Data will be open access. |
| **Available for what types of analyses?** | Data will be available for any purpose including meta-analyses. |
| **How or where can data be obtained?** | Data will be deposited in the La Trobe University library repository. |
| **What supporting documents are/will be available?** | Study protocol<br>Ethical approval |

## How or where can supporting documents be obtained?

| | |
|---|---|
| Type [1] | Ethical approval |
| Citation [1] | |
| Link [1] | |
| Email [1] | |
| Other [1] | |
| Attachment [1] | /Steps11and12/377484-(Uploaded-08-07-2019-12-31-15)-Study-related document.pdf |
| Type [2] | Study protocol |
| Citation [2] | |
| Link [2] | |
| Email [2] | |
| Other [2] | We aim to publish a study protocol in an open access journal. |
| Attachment [2] | |

## Summary results

No Results

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# Participant Information Sheet/Consent Form – Parent/Guardian

**Interventional Study** - *Parent/Guardian consenting on behalf of participant*

| | |
|---|---|
| **Title:** | Improving muscle strength in young people with Prader-Willi syndrome: a phase II randomised trial |
| **Short Title** | Exercise for people with Prader-Willi syndrome (PRESTO trial) |
| **Project Sponsor** | La Trobe University |
| **Principal Investigator** | Prof Nora Shields |
| **Associate Investigator(s)** | Prof Kim Bennell<br>Prof Nicholas Taylor<br>Dr Lauren Rice<br>A/Prof Tania Markovic<br>Prof Chris Bigby<br>A/Prof Jenny Watts<br>A/Prof Luke Prendergast |

## Part 1 What does the young person's participation involve?

### 1 Introduction

This is an invitation for the young person in your care to take part in this research project. The young person is being invited to take part because they have Prader-Willi syndrome. In this project we want to find out if it would be helpful for young people with Prader-Willi syndrome to do exercise.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want the young person to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not the adolescent or young adult can take part, you might want to talk about it with a relative, friend or the adolescent or young adult's local doctor.

### 2 Do I have to take part in this research project?

**Participation is voluntary**
The young person's participation in this study is completely voluntary and there will be no cost to you or the young person. If you do not want the young person to take part in this study they do not have to. They should feel under no obligation to participate in this study. Choosing not to take part in this study will not affect their current and future medical care in any way.

If you decide you want the young person to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent to the young person taking part in the research project

• Consent for the young person to have the tests and treatments that are described
• Consent to the use of the young person's personal and health information as described, including the young person's Medicare Benefits Schedule (MBS) and/or Pharmaceutical Benefits Scheme (PBS) data.

**Your withdrawal from the study**
The young person is under no obligation to continue with the research study. They may change their mind at any time about participating in the research. People withdraw from studies for various reasons and they do not need to provide a reason.

You can withdraw the young person from the study at any time by completing and signing the **'Form for Withdrawal of Participation – Parent/Guardian'**. This form is provided at the end of this document and is to be completed by you and supplied to the research team if you choose to withdraw the young person at a later date.

If you withdraw the young person from the study, you will be able to choose whether the researchers will destroy or retain the information they have collected about the young person. You should only choose **one** of these options. Where both boxes are ticked in error or neither box is ticked, the study will destroy all MBS and PBS information it has collected about the young person.

You will be given a copy of this Participant Information and Consent Form to keep.

## 3 What is the purpose of this research?

In this study we want to find out if doing exercise for 6 months at a community gym is good for young people with Prader Willi syndrome aged 13 years and over.

Exercise is considered an important part of the treatment of Prader-Willi syndrome. However, very little is known about what type of exercise is best for people with Prader-Willi syndrome. We also don't know much about what helps people with Prader-Willi syndrome to exercise. This project will help us understand what type of exercise is good for people with Prader-Willi syndrome and how to support people with Prader-Willi syndrome to exercise in their community.

## 4 What does participation in this research involve?

The young person will be taking part in a project called a double-blind, randomised controlled research project. This means we will put the young person into one of two groups, but they will not know which group they are in. The young person will be put into a group by chance. They have a 50/50 chance of being in each group.

Each group will get a different exercise program. Both groups will exercise at a community gym. Both groups will be supervised by an exercise professional, who will usually be a physiotherapist or a personal trainer. Both groups will exercise twice a week for 24 weeks. The researchers will know which exercise program the young person is getting. We will compare the results of the groups to see which exercise program is better.

### *(i) What does the exercise program involve?*

The young person will be asked to do an exercise program for 24 weeks. The young person will exercise 2 times each week for about 1 hour. The young person will do the exercise program at a community gym. The gym will be close to where the young person lives.

The young person will also receive 2 exercise planning sessions after their exercise program. The young person will do one planning session 1 month after they finish their exercise program and one planning session 3 months after they finish their exercise program. Each session will go for about 1 hour.

An exercise professional will help the young person to do the exercise program. The health professional will probably be a physiotherapist or a personal trainer. This person will write down things about the young person's exercise program in a diary or iPod. They will write down things like:

- how many exercise sessions the young person did,
- what exercises the young person did,
- if there were any problems with exercising,
- if the young person talked to other people at the gym

We will give the exercise professional an iPod at the start of the exercise program. The exercise professional will assist the young person to use the iPod to take photographs to tell us about the exercise program. The young person might take photographs of things they like or dislike about the exercise program. The young person will be asked to record short videos to tell short stories about things that happened at the gym. The young person will use these photographs and videos to help them tell their story to the researcher during an interview with one of the researchers. This interview will take place after the young person finishes the exercise program. The interview can be done face-to-face, by telephone or by videoconference. In the interview the young person will talk about their experiences exercising at the gym. The interview will take about 20 minutes. We will record the interview so we can listen to the answers later. The young person can ask to end the interview at any time.

You will also be invited to do an interview with one of the researchers. You will be asked to talk about what you think about the young person doing an exercise program at the gym. The young person can choose if they would like to do the interviews separately or together with you.

If the young person lives in Victoria, they may have a researcher come and watch between three and five of the exercise sessions. The researcher will make notes to describe what happened during the exercise session, such as who was in the gym, and if the young person spoke with other people at the gym.

***(ii) What tests will we be asked to do?***

The young person will need to do some tests if they take part in this project. The young person will do these tests before the start the exercise program, at the end of the exercise program and 6 months after the exercise program.

The young person will be asked to do the following tests at each testing visit:

| | Test | How we do the test |
|---|---|---|
| **1** | *Muscle strength* | Measures how much weight the young person can lift or push with their arms and legs |
| **2** | *Muscle size* | A whole body scan called a DXA scan will be done. A DXA scan is a type of x-ray. The young person will need to lie down on the machine that does the scan. They will need to be still for about 15 minutes while the scan is being done. The scan measures the size of their muscles. Their waist circumference, weight and height will be measured before this test. |
| **3** | *Timed stairs test* | Measures how long it takes the young person to go up and down a flight of stairs |
| **4** | *Box stacking* | Measures how many boxes the young person can stack in one minute |
| **5** | *Sit to stand test* | Measures how long it takes the young person to stand up and sit down 5 times |
| **6** | *6-minute walk* | Measures how far the young person can walk in 6 minutes |

| | | |
|---|---|---|
| **7** | *Physical activity* | The young person will be asked to wear a small monitor for 8 days on their waist to measure the amount of movement they do. |
| **8** | *Physical activity recall questionnaire* | Asks questions about what sports, games and other physical activities the young person does, how many times a week the young person does these activities and how long the young person spends doing these activities.<br>You may help the young person answer the questions. |
| **9** | *Sedentary activity questionnaire* | Asks questions about 12 sedentary activities the young person might do and how often they do them during the week and at the weekends.<br>You can help you the young person answer the questions. |
| **10** | *Participation and environment measure (community section)* | Asks questions about 10 community activities the young person might do and how involved they are in those activities. There are also questions about the young person's community, and what makes it easier or harder for them to take part in the community.<br>You can help the young person answer the questions. |
| **11** | *Child Health Utility questionnaire* | Asks 9 questions about the young person's quality of life. The young person will answer the questions on this form themselves if they can.<br>You can help the young person answer the questions if they have difficulty answering themselves. |
| **12** | *Quality of life Inventory- Disability questionnaire* | Asks 42 questions about the young person's quality of life.<br>This form is answered by you. |
| **13** | *Developmental behaviour checklist* | Asks 96 questions about your behaviour.<br>This form is answered by you. |
| **14** | *Health utilisation* | We want to find out if the exercise program is value for money. To do this we will collect information about the young person and their family such as where they work or go to school, how much money they earn, what help they need from other people, how much it costs them to do the exercise program and how often they see a health professional such as your GP or physiotherapist.<br>This form is answered by you. |
| **15** | *Diet* | You will be asked to fill in a survey about the young person's diet. It will take about 15 minutes. |

***(iii) Where will the tests be done? How long will the testing session take?***

We will do the testing sessions at:

- La Trobe University, Melbourne campus in Bundoora, in Melbourne, Victoria;
- CPC RPA Clinic, Boden Institute, Charles Perkins Centre at the University of Sydney in Camperdown, in Sydney, New South Wales
- Princess Alexandra Hospital, in Brisbane, Queensland.

When there are circumstances that mean a young person cannot travel to one of the above assessment sites, we will organise for the assessments to be done as close as possible to where the young person lives.

Each testing session will take about 2 hours. The young person will need to get themselves to the place where the tests are done.

***(iv) Who else will know the young person is taking part?***

If the young person decides to take part in this project, we will tell their general practitioner or GP.

***(v) What else do I need to know?***

You will be asked to sign a consent form before the young person takes part in the project.

We will also seek your permission to contact Services Australia to find out about the young person's use of medical services and medicines over a 12-month period since taking part in the study.

If you are parent or carer of a young person who is aged between 14-17 years old and do not have a legal guardianship order in place, we will ask you to provide additional documentation to support your permission to contact Services Australia.

(1) a letter from your GP or other suitable health professional stating your young person lacks capacity to make their own medical decisions;
(2) identification documents for both yourself and your young person;
(3) a statutory declaration signed by a Justice of the Peace or equivalent stating you are the best person to have access/control of your young person's records and confirming your relationship to the young person.

Where a child under 14 years of age is on two Medicare cards, both card numbers and the signatures of both primary card holders will need to be on the child's consent form. Data relating to a child's Medicare card will only be supplied where the primary card holder of that card has consented.

You will be asked to sign a consent form authorising the study to access the young person's complete Medicare Benefits Schedule and/or Pharmaceutical Benefits Scheme data as outlined in the consent form. The data we will ask for this study will be for the 12-month period since they took part in the study.

Medicare Benefits Schedule collects information on the young person's doctor visits and the associated costs, while the Pharmaceutical Benefits Scheme collects information on the prescription medications they had filled at pharmacies. The consent form is sent securely to Services Australia who holds Medicare Benefits Schedule and Pharmaceutical Benefits Scheme data confidentially.

The young person's Medicare Benefits Schedule and Pharmaceutical Benefits Scheme data will only be used for the purpose of this research project, these data cannot be used in future research outside of this approved project. However, future research projects that are extensions of or closely related to this project may use other information collected for this project. This information will only be disclosed with your permission, except as required by law. Further, your consent is only specific to participation in this and closely related research projects and does not involve the establishment of a databank.

The young person can continue to do their other usual activities while taking part in the project. The young person will need to tell us what other activities they do. We will let them know if there's an activity they can't do.

## 5 What does it cost?

The young person does not have to pay to take part in this project.

We will:

- Cover the cost of the gym membership for 6 months
- Pay the exercise professional who will help the young person do the exercise program
- Pay $100 in vouchers for attending the testing session
- If the young person lives interstate, we will cover the cost of flights, accommodation and getting to and from the airport up to $1000.

Money will usually be paid to the parent or guardian on behalf of the young person unless you tell us otherwise.

## 6 Other relevant information about the research project

Sixty young people with Prader-Willi syndrome from Australia will be taking part in this project. There are three testing centres in Melbourne, Sydney and Brisbane. People with Prader-Willi syndrome who live outside of these places can take part if they are willing to travel to Melbourne, Sydney or Brisbane to do their tests. We will provide money to people who need to travel to attend their testing sessions.

This project is being done by researchers and health professionals from the following places: La Trobe University, Melbourne; University of Melbourne; University of Sydney; Deakin University, Melbourne; University of Queensland; Royal Children's Hospital, Melbourne; Austin Hospital, Melbourne; Royal Prince Alfred Hospital, Sydney; Queensland Children's Hospital, Brisbane; Princess Alexandra Hospital, Brisbane.

## 7 What are the possible benefits of taking part?

We cannot promise that the young person will receive any benefits from taking part in this project. The young person might find doing exercise improves their fitness. The young person might find their muscles get stronger. The young person might find doing everyday activities might be easier. The young person might enjoy exercising at the gym. The young person might like that they are helping other people with Prader-Willi syndrome by taking part.

## 8 What are the possible risks and disadvantages of taking part?

Exercise can sometimes cause side effects. The young person may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If the young person has any of these side effects, or are worried about them, talk with the researcher. The researcher will also be looking out for side effects.

The risks to the young person are most likely to happen when they start exercising. The most common side effect after starting to exercise is that the young person's muscles get sore. This can happen 1 or 2 days after starting exercise. Sore muscles usually get better quickly and having muscle soreness does not usually stop the young person from exercising again. The researchers will try and minimise the risk of the young person getting muscle soreness by having an exercise professional supervise the exercise program. The exercise professional will help the young person to exercise in the correct way and to use the gym equipment that suits them best. The researcher will tell the young person the best way of easing muscle soreness.

Other side effects that may occur when the young person starts to exercise in the gym may be anxiety about meeting a new person or being in a new place. The exercise professional who will be helping the young person with the exercise program will give them as much support as they need to feel comfortable. The exercise professional will do some training before they start working with the young person to learn about Prader-Willi syndrome. The young person will be encouraged to tell the exercise professional straight away if they feel unwell or uncomfortable when exercising. You or a carer are welcome to attend the exercise sessions with the young person if this will help them.

Many people with Prader-Willi syndrome can have a temper outburst (sometimes called a meltdown) which can happen in any place. It is possible the young person might have a temper outburst when they are doing their exercise program. The exercise professional working with the young person will do their best to communicate clearly with them to help prepare them for what to expect during the exercise program and to signal any changes to the program. They will treat the young person fairly, will avoid rushing them and will do their best to understand what the young person is saying. They will also make sure the young person is safe if they do have a temper outburst and will give them space to calm down.

While the young person is exercising, they will have to work hard and they will likely sweat. The young person will be given time between exercises, if they need to rest.

There may be side effects the researchers do not expect or do not know about and that may be serious. The young person should tell the researchers immediately about any new or unusual symptoms they get. Many side effects go away shortly after exercising. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, the researcher may need to stop the young person from exercising.

This research project involves exposure to a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this research project is about 0.03mSv. At this dose level, no harmful effects of radiation have been demonstrated, as any effect is too small to measure. This risk is believed to be minimal.

Has the young person been involved in any other research studies that involve radiation? If so, please tell us. Please keep information contained within this participant Information and consent form about the young person's exposure to radiation in this study, including the radiation dose for 5 years. You will need to provide this information to researchers of any future research projects involving exposure to radiation.

## 9 Can the young person have other treatments during this research project?

While the young person is taking part in this research project, they can continue to take all their medications or receive their usual medical treatment for their condition or for other reasons. It is important to tell the researchers about any treatments or medications the young person may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell the researcher about any changes to these while the young person is taking part in the research project.

If possible, the young person will be asked not to change their medications while they are in the study. This includes starting on growth hormone therapy. If the young person needs to change their medications during the study, we will ask you to let us know what changes were made so that we can note this.

## 10 What if I withdraw the young person from this research project?

If you withdraw the young person from the study, the researchers will stop paying for the gym membership that the young person received so that they could exercise at the gym as part of the study.

## 11 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

- Unacceptable side effects
- The treatment being shown not to be effective
- The treatment being shown to work and not need further testing

### 12 What happens when the research project ends?

Within approximately 6 months of the study finishing, the researchers will send a written summary report about the study to the people who took part. If the young person wants a copy of their individual results they will be given these upon written request to the researchers.

## Part 2 How is the research project being conducted?

### 13 What will happen to information about the young person?

In this study we will collect and use personal and health information about the young person for research purposes. We can disclose this information only with your permission, except as required by law.

Information about the young person may be obtained for the purpose of this project from their health records at the hospital where they usually visit their doctor (e.g. Royal Children's Hospital, Melbourne; Austin Hospital, Melbourne; Royal Prince Alfred Hospital, Sydney; Queensland Children's Hospital, Brisbane; Princess Alexandra Hospital, Brisbane). By signing the consent form, you agree to the researchers accessing the young person's health records if it is relevant to their participation in this research project. Information about the young person's participation in this research project may be recorded in your health records.

The young person's information will be used for this research project. We may use the young person's data in future research projects that are closely related to this project.

The following people may access the young person's personal and health information as part of this research project. The:

- research team involved with this project
- Royal Children's Hospital Human Research Ethics Committee who approved the project

The researchers (their names are listed at the start of this document) will have access to the young person's data. In instances where other researchers will need to access the young person's data for future research projects, the University Human Ethics Committee will be advised and requested to grant permission to do so, except as required by law.

We will store the young person's information securely at La Trobe University. We will store the electronic information on secure databases at La Trobe University. We will store the physical information in a locked filing cabinet in the office of Prof Nora Shields at La Trobe University during the project and in a locked archive at La Trobe University after the results of the project have been published.

The young person's information will be identifiable by the researchers. This means the young person's name and other personal details will stay on the information while it is used by the research team. The young person will be given a code number, which will be used when entering data on the computer. Although the researchers will know who the young person is during the project, their name will not be included as part of the results of the project. The young person's identity will remain confidential.

De-identified data from the project will be deposited in the La Trobe University library repository. No one apart from the researchers will have access to re-identifiable data.

We plan to publish the results of this research project in journals and to present them in a variety of places such as at conferences and in workshops. The presentations could take place

in Australia or overseas. The young person's information will be grouped together with the other participants in the project. We will present the findings from the project in such a way that the young person cannot be identified unless you say it is ok for us to do so. If you agree to let us use photographs of you in public presentations, then you could be identified in those pictures.

You have the right to access and to correct the information we collect and store about the young person. This is in accordance with relevant Australian and/or Victorian privacy and other relevant laws. Please contact us if you would like to access this information.

In accordance with regulatory guidelines, the Medicare Benefits Schedule and Pharmaceutical Benefits Scheme data and all other data collected for this project will be kept for 15 years, and then it will be securely destroyed. Paper based data will be put in confidential waste bins available at La Trobe University. Electronic data will be deleted.

## 14 Complaints and Compensation

If the young person suffers any injuries or complications as a result of this research project, you should contact the research team as soon as possible and you will be assisted with arranging appropriate treatment. If the young person is eligible for Medicare, they can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

If you have any questions or complaints about this project you can telephone Prof Nora Shields at La Trobe University, on 03 9479 5852. If you have any complaints or questions that the researchers has been unable to answer, you may contact Alexandra Robertson at the Royal Children's Hospital Human Research Ethics on 03 9345 6924.

## 15 Who is organising and funding the research?

This research project is being conducted by Prof Nora Shields from La Trobe University, Melbourne. The project is being funded by the Medical Research Future Fund of Australia ($869,140).

No member of the research team will receive a personal financial benefit from the young person's involvement in this research project (other than their ordinary wages).

## 16 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Royal Children's Hospital, Melbourne.

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

## 17 Further information and who to contact

If you want any further information concerning this project or if the participant has any medical problems which may be related to their involvement in the project (for example, any side effects), you can contact the principal researcher, Nora Shields, Professor of Physiotherapy at La Trobe University on 03 9479 5852 or n.shields@latrobe.edu.au

For matters relating to research at the site at which the young person is participating, the details of the local site complaints person are:

**Complaints contact person**

| | |
|---|---|
| Name | Dr Zoe McCallum |

| | |
|---|---|
| Position | Consultant Paediatrician, Department of Neurodevelopment and Disability, Royal Children's Hospital |
| Telephone | 03 9345 5522 |
| Email | zoe.mccallum@rch.org.au |

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

**Reviewing HREC approving this research and HREC Executive Officer details**

| | |
|---|---|
| Reviewing HREC name | Royal Children's Hospital Human Research Ethics Committee |
| HREC Executive Officer | Alexandra Robertson |
| Telephone | 03 9345 6 |
| Email | alexandra.robertson@rch.org.au |

If you have a privacy complaint in relation to the use of your Medicare Benefits Schedule (MBS) and/or Pharmaceutical Benefits Scheme (PBS) data you should contact the Office of the Australia Information Commissioner. You will be able to lodge a complaint with them.

Website: www.oaic.gov.au
Telephone: 1300 363 992
Email: enquiries@oaic.gov.au
Mail: GPO Box 5218, Sydney NSW 2001

# Consent Form – Parent/Guardian

| | |
|---|---|
| **Title:** | Improving muscle strength in young people with Prader-Willi syndrome: a phase II randomised trial |
| **Short Title** | Exercise for people with Prader-Willi syndrome (PRESTO trial) |
| **Project Sponsor** | La Trobe University |
| **Principal Investigator** | Prof Nora Shields |
| **Associate Investigator(s)** | Prof Kim Bennell<br>Prof Nicholas Taylor<br>Dr Lauren Rice<br>A/Prof Tania Markovic<br>Prof Chris Bigby<br>A/Prof Jenny Watts<br>A/Prof Luke Prendergast |



## Declaration by Parent/Guardian

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for the young person's doctors, other health professionals, hospitals or laboratories outside this hospital to release information to La Trobe University concerning the young person's condition and treatment including details about their medical visits and prescriptions for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to the young person participating in this research project as described and understand that I am free to withdraw them at any time during the research project without affecting their future health care.

I understand that I will be given a signed copy of this document to keep.

Name of the young person (please print) _____

Signature of the young person _____ Date _____

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date _____

## Declaration by Researcher

I have given a verbal explanation of the research project, its procedures and risks and I believe that the parent/guardian has understood that explanation.

Name of Researcher (please print) _____

Signature _____ Date _____

# Form for Withdrawal of Participation – Parent/Guardian

| | |
|---|---|
| **Title:** | Improving muscle strength in young people with Prader-Willi syndrome: a phase II randomised trial |
| **Short Title** | Exercise for people with Prader-Willi syndrome (PRESTO trial) |
| **Project Sponsor** | La Trobe University |
| **Principal Investigator** | Prof Nora Shields |
| **Associate Investigator(s)** | Prof Kim Bennell<br>Prof Nicholas Taylor<br>Dr Lauren Rice<br>A/Prof Tania Markovic<br>Prof Chris Bigby<br>A/Prof Jenny Watts<br>A/Prof Luke Prendergast |

**Declaration by Parent/Guardian**

I wish to withdraw the young person from participation in the above research project effective from the date below.

Please tick one of the following boxes:

1. ☐ I wish to withdraw the young person from participation and have all their information destroyed from the whole study where possible, including all my Medicare Benefits Schedule (MBS) and/or Pharmaceutical Benefits Scheme (PBS) claims and have no further participation.

2. ☐ I wish to withdraw the young person from participation and have all their Medicare Benefits Schedule (MBS) and/or Pharmaceutical Benefits Scheme (PBS) claims a destroyed from the study where possible, but I am happy for all other information about the young person to be used in the study.

3. ☐ I wish to withdraw the young person from participation but allow all the young person's information including all their Medicare Benefits Schedule (MBS) and/or Pharmaceutical Benefits Scheme (PBS) claims collected up to the withdrawal date to continue to be used in the study.

I understand that:

4. no further information about the young person will be collected for the study from the withdrawal date;

5. the young person's information that has already been collected, and analysed and/or included in a publication, may not be able to be withdrawn or destroyed; and

6. the young person's withdrawal from the study will not affect their routine treatment, their relationship with those treating them or their relationship with La Trobe University.

If you wish to tell us the broad reason why the young person is no longer taking part in the study, please tick the relevant box below:

☐ No longer interested

☐ Circumstances have changed and no longer in a position to take part

☐ Cannot commit the time to take part

☐ There is a medical reason for withdrawing

☐ Other (please specify)……

Name of the young person (please print) _____

Signature of the young person _____ Date _____

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date _____

In the event that the parent/guardian's decision to withdraw is communicated verbally, the researcher will provide a description of the circumstances below.

**Declaration by Researcher†**

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the parent/guardian has understood that explanation.

Name of Researcher† (please print) _____

Signature _____ Date _____

Note: All parties signing the consent section must date their own signature.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

| Section/item | ItemNo | Description | Manuscript location |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | p. 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | p.3 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | p.1, 3-14; Figure 1, Table 1 and 2 |
| Protocol version | 3 | Date and version identifier | Appendix 1 |
| Funding | 4 | Sources and types of financial, material, and other support | p.15 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | p.1; 15-16 |
| | 5b | Name and contact information for the trial sponsor | n/a |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | p.15 |
| | 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) | p.13 |
| **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 | p.4-5 |
| | 6b | Explanation for choice of comparators | n/a |
| Objectives | 7 | Specific objectives or hypotheses | p.5 |

| | | | |
|---|---|---|---|
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | p.5 |
| **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 | p.5-6 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | p.5 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | p.6-8 |
| | 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) | p.6 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | p.6 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | p.6 |
| 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 | p.8-9 Table 2 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Figure 1 |
| 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 | p.12 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | p.6 |

**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 | p.5 |
| 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 | p.5 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | p.5 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | p.6 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | n/a |

**Methods: Data collection, management, and analysis**

| | | | |
|---|---|---|---|
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | p.8-9, Table 2 |
| | 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 | p.12 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | p. 12-14 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | p.12-13 |

| | | | |
|---|---|---|---|
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | p.12-13 |
| | 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) | p.12 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | p.13 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | P 9, Table 2 |
| 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 | p.13-14 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | p. 13 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | p.13-14 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | p.14 |

| | | | |
|---|---|---|---|
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | p.15 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | p.15 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | n/a |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | p.14 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | n/a |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | p.15 |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Not included for submission but can be provided upon request |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a |

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

BMJ Open

# Progressive resistance training in young people with Prader-Willi syndrome: protocol for a randomised trial (PRESTO)



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|---|---|
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| Secondary Subject Heading: | Rehabilitation medicine |
| Keywords: | Developmental neurology & neurodisability < PAEDIATRICS, Clinical trials < THERAPEUTICS, PUBLIC HEALTH, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT |
| | |

**TITLE:** Progressive resistance training in young people with Prader-Willi syndrome: protocol for a randomised trial (PRESTO)

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## ABSTRACT

**Introduction:** Preliminary evidence suggests progressive resistance training may be beneficial for people with Prader-Willi Syndrome (PWS), a rare genetic condition that results in muscle weakness and low muscle tone.

**Aims**: To establish if community-based progressive resistance training is effective in improving the muscle strength of people with PWS; to determine cost-effectiveness; and, to complete a process evaluation assessing intervention fidelity, exploring mechanisms of impact, understanding participant experiences and identifying contextual factors affecting implementation.

**Methods and analysis:** A multisite, randomised controlled trial will be completed. Sixty participants with PWS will be randomised to receive either progressive resistance training (experimental) or non-progressive exercise (placebo-control). Participants will be aged 13 to 60 years, be able to follow simple instructions in English, and have no contraindications to performing progressive resistance training. The experimental group will complete progressive resistance training twice weekly for 24 weeks supervised by an exercise professional at a community gym. The control group will receive all aspects of the intervention except progressive overload. Outcomes will be assessed at week 25 (primary endpoint) and week 52 by a blinded assessor. The primary outcome is muscle strength assessed using one repetition maximum for upper limb and lower limb. Secondary outcomes are muscle mass, functional strength, physical activity, community participation, health-related quality of life and behaviour. Health economic analysis will evaluate cost-effectiveness. Process evaluation will assess safety and intervention fidelity, investigate mechanism of impact, explore participant experiences and identify contextual factors affecting implementation. Data collection commenced in February 2020 and will conclude in September 2023.

**Ethics and dissemination**: Ethical approval was obtained from The Royal Children's Hospital Human Research Ethics Committee (HREC/50874/RCHM-2019) under the National Mutual Acceptance initiative. Research governance approvals were obtained from five clinical sites. Results will be disseminated through published manuscripts, conference presentations, public seminars and practical resources for stakeholder groups.

**Trial registration** Australian and New Zealand Clinical Trial Registry (ACTRN12620000416998).


**Strengths and limitations of this study:**

- Multisite randomised controlled trial recruiting participants from across Australia to investigate the effectiveness of progressive resistance training for people with Prader-Willi Syndrome on muscle strength (primary outcome), muscle mass, functional strength, physical activity, behaviour and participation.
- Inclusion of an embedded health economic analysis will evaluate cost-effectiveness of progressive resistance training from healthcare and societal perspectives, with outcomes based on muscle strength (primary outcome) and health-related quality of life (secondary outcome).

- An embedded process evaluation will assess intervention safety and fidelity, mechanism of impact, participant experiences and contextual factors affecting implementation.
- Participants and assessors will be blinded to group allocation, however it is not possible to blind exercise professionals. Quantitative data analysis will be blinded.

## INTRODUCTION

Prader-Willi syndrome (PWS) is a rare condition with extensive musculoskeletal sequelae resulting from a genetic abnormality on chromosome 15 at q11–13.[1] Approximately 400,000 people live with PWS worldwide.[2] In combination with hyperphagia (uncontrolled urge to eat), intellectual disability,[3] emotional outbursts[4] and anxiety,[5] PWS can result in premature death[6] due to extreme obesity.[7, 8] Limited treatments exist and health care costs are high; estimated in 2016 to be €60k per individual per annum.[9],[10],[11]

The musculoskeletal features of PWS include abnormal growth and body composition.[12] People with PWS have very low lean body mass, muscle weakness and hypotonia. Their muscle mass is 25 to 40% lower and their muscle strength approximately 70% lower than those without PWS. This has detrimental effects on physical functioning, causing severe delay in childhood motor development and persistent mobility problems in adulthood.[12] Approximately 90% of people with PWS require assistance with activities of daily living.[13] For people with PWS, muscle weakness, hypotonia and poor motor proficiency can reduce the desire to be active,[14] leading to a cycle of sedentary behaviour, deteriorating muscle function, obesity, greater metabolic risk, social isolation, lower quality of life,[15] and early mortality.[3] Increasing muscle strength in a program sufficiently long to establish an exercise routine and behaviour change has the potential to have clinical impact for people with PWS by improving their mobility, making it easier to perform activities of daily living and physical activity.

The musculoskeletal features of PWS also adversely impact metabolic function. Having very low muscle mass limits the ability to balance increased energy intake due to hyperphagia, making weight control difficult. Medications to increase muscle mass are either ineffective[16] or expensive. Usual care in PWS comprises aerobic exercise and a strictly controlling diet. However, aerobic exercise targets cardiovascular fitness rather than increases in muscle strength or muscle mass and so does not directly address altered body composition. Aerobic exercise also requires coordination, concentration and time commitment, which can affect adherence and make it difficult for those with mobility problems, complex behavioural issues and intellectual disability.

Muscle strength and muscle mass are increased by progressive resistance training (strength training) in the general[17] and other disability populations,[18] when implemented with sufficient intensity and progression of load.[19] No trials have investigated the effect of progressive resistance training in people with PWS, so it is unclear if it will have the intended effect given the genetic basis to their muscle weakness (their muscles may not adapt to training) and their complex behavioural issues could be a substantial threat to regular exercise adherence. Progressive resistance training requires high loads to be lifted for a low number of repetitions before muscular fatigue, with load progression as the person gets stronger. Preliminary evidence from three small studies in children[20, 21] and adults with PWS,[22] demonstrate proof-of-principle that muscle strengthening exercise can increase strength[22] and muscle mass,[20],[21] leading to improvements in walking[22] and physical activity.[20] However, in these studies the training was usually not progressed; was home-based requiring parental supervision; and, the research designs lacked rigour due to no randomisation, control groups, or blinded assessment. A recent randomised feasibility trial ($n$=16) of a 10-week program supervised by a physiotherapist successfully implemented progressive resistance training with excellent attendance (92%) and adherence (82%) and few minor adverse events.[23] Estimates of effect were moderate to large in favour of progressive resistance

training compared to a waitlist control group. A qualitative study conducted alongside the trial found the supervising physiotherapists perceived progressive resistance training achieved important clinical outcomes related to fostering independence and confidence in the participants with PWS. Thus, increasing muscle strength in young people with PWS could mean less need for assistance with activities of daily living (reducing carer burden and costs) and improved ability to participate in physical activity, improving health and reducing obesity-related comorbidity. Establishing an exercise routine may also provide the impetus to ongoing participation in regular physical activity.

Therefore, our primary aim is to establish if 6-months community-based progressive resistance training is effective in improving the arm and leg muscle strength of people with PWS. Our secondary aims are to:
(i) determine if progressive resistance training leads to changes in muscle mass, functional strength physical activity, community participation, health-related quality of life and behaviour;
(ii) determine if progressive resistance training is cost-effective in people with PWS; and
(iii) complete a process evaluation that assesses intervention safety and fidelity, explores mechanisms of impact, understands participant experiences, explores contextual factors affecting implementation and identifies pragmatic strategies for successful implementation of progressive resistance training in those with intellectual disabilities and behavioural challenges.

## METHODS AND ANALYSIS

### Trial design

A multisite, parallel-group randomised controlled trial (RCT) with follow-up at one year, and embedded health economic and process evaluations, will be conducted. Participants with PWS will be randomly allocated to either the experimental group (progressive resistance training) or a placebo-control group (non-progressive exercise) (Fig 1). Randomisation will be in a 1:1 ratio with stratification by trial location (VIC, NSW or QLD) and minimisation (by age, sex, type of PWS and receipt of growth hormone therapy) with a random component of 80%. Randomisation will occur after eligibility has been determined, the participant has consented, and a baseline assessment completed. Randomisation will be coordinated by Griffith University Randomisation Service, Queensland, Australia. The trial has been registered prospectively, including updates, with the Australian and New Zealand Clinical Trial Registry (online supplemental appendix 1).

### Participants

To be eligible for inclusion, participants must meet the following criteria:
(1) have genetically confirmed PWS, and live in Australia;
(2) aged between 13 and 60 years; and,
(3) able to follow verbal instructions in English.

People will be excluded if they:
(1) have participated in progressive resistance training in the 3 months prior to randomisation; or,
(2) have a concurrent physical or mental health condition (e.g., severe arthritis, severe psychosis, physically aggressive behaviour) affecting their ability to participate in community-based exercise.

**Recruitment**

Participants will be recruited through four sources:

(i) Population registries or clinical databases (e.g. Victorian PWS register; Global PWS Registry; and the Australian National PWS database). Custodians of these databases will send a copy of the trial advertisement to potential participants.

(ii) Specialist PWS clinics in Melbourne, Sydney, and Brisbane. Potential participants will be informed of the trial by their treating doctor or therapist.

(iii) PWS advocacy groups based in Australia will send a copy of the flyer advertising the trial to their members.

(iv) Parent and carer networks (including social media groups): research team members who are parents of people with PWS will disseminate information about the trial to their personal networks and through parent and carer forums.

Prospective participants or their caregiver will complete a screening process by telephone with a research team member to assess their eligibility for the trial, including the completion of a pre-exercise screening questionnaire (PAR-Q+).[24] If any concerns related to suitability to take part are identified, they will be asked to obtain medical clearance prior to enrolment (e.g. unexplained symptoms such as chest pain or shortness of breath at rest).

**Intervention**

All participants will continue to receive their usual health care, which will be documented. All participants will complete an exercise program and will be blinded to their group allocation.

*Experimental group*

Participants allocated to the experimental group will complete progressive resistance training twice a week for 24 weeks at a community gymnasium (Table 1). The program, designed according to American College of Sports Medicine guidelines,[17] will comprise 6 exercises: 3 for the upper limbs (e.g. lat pull down) and 3 for the lower limbs (e.g. seated calf raise). Exercises will be performed on pin-loaded weight machines, as these are safer for novices than free weights. Exercises can be modified to suit the availability of equipment at a particular gym. Participants will perform up to 3 sets of 12 repetitions of each exercise until fatigue (intensity of 60-80% of 1 repetition maximum, 1RM). A 2-minute rest will be taken between each set to allow recovery, and resistance will be increased when 3 sets of 12 repetitions of an exercise can be completed. Each training session will last approximately one hour.

Participants will be supervised 1:1 by an exercise professional (Table 1). Supervision will ensure participants exercise at the correct intensity, provide physical and motivational support, and limit participant access to food.[25] The supervising professional will document the program in an online exercise logbook (including exercises performed, weight lifted, number of repetitions and sets). Supervisors will be invited to participate based on their location. They will receive training on the trial protocol, specialist advice on PWS, facilitating exercise in people with PWS, communication strategies, and proactively managing PWS behaviours such as emotional outbursts. The supervisor training will be delivered via a university online learning site and a printed training manual.

Table 1. Description of experimental and control group interventions according to the template for intervention description and replication (TIDieR)[26]

| | Experimental group | Control group |
|---|---|---|
| Brief name | Progressive resistance training | Non-progressive training |
| Why | To increase muscle strength | To exercise in a way that would not be expected to increase muscle strength |
| What materials | Exercise professional maintains an online logbook to record the content of each session (e.g. exercises performed, weight lifted, number of repetitions and sets) and any adverse events | |
| What procedures | To follow progressive resistance training principles: (1) exercise at sufficient intensity (60-80% of 1 repetition maximum), progressive overload (increase resistance as participant gets stronger) and allow recovery (1-2 minutes between exercise sets and at least one day between sessions) | To commence training with no resistance and progresses to 10% of 1RM (a level insufficient to increase muscle strength). It will remain at this load during the entire program |
| Who provided | An exercise professional (e.g. physiotherapist, exercise physiologist or personal trainer) who has completed an online training module. | |
| How provided | Training will be supervised 1:1 and will usually use pin-loaded weight equipment | |
| Where (setting) | At a community gymnasium local to each participant | |
| When/how much (dose) | 48 sessions each of 60 minutes duration over 24 weeks (total 48 hours) | |
| Tailoring | Resistance will be tailored to the individual (60-80% of their 1 repetition maximum of each exercise). | If necessary, to maintain a participant's interest, skills-based exercise may be incorporated into the program |
| Fidelity checking measures | Adherence to the protocol parameters of attendance, exercise type, intensity and volume, rest periods, and program frequency, duration and progression documented at each session in an online logbook (using REDCap software) | |

*Control group*

Participants allocated to the control group will receive all aspects of the intervention (same setting, supervision, equipment, number of repetitions and sets, duration and frequency). However, participants will exercise at a low intensity, with no progressive overload of muscles. Exercise training will commence using no resistance and will progress to 10% of 1RM (a level insufficient to increase muscle strength) and will remain at this load during the program. This design has been implemented successfully in another trial,[27] allowing attribution of any between group differences to progressive resistance training and not other factors such as therapist attention.

Both groups will be offered two 1-hour planning sessions for participants and their caregivers after the week 25 assessment to discuss continued participation in community-based exercise. Informed by the Health Action Process framework,[28] these sessions will aim to address barriers to community participation and may include information on accessing available resources to support ongoing exercise participation. The content of these sessions will be individualised. The first session will be completed within four weeks and the second session within 12 weeks of program completion.

**Outcome measures**

Outcomes will be assessed at weeks 0 (baseline), 25 (immediately after the intervention; primary endpoint) and 52 by an assessor blind to group allocation (Table 2). Assessments will take place at three sites (Melbourne, Sydney, Brisbane).

*Primary outcome measure*

Muscle strength will be assessed using 1 repetition maximum (1RM) force generation tests for upper limb and lower limb, respectively. These tests establish the amount of weight each participant can lift in a single seated chest press and leg press respectively. Single 1RM chest and leg press tests have high levels of retest reliability ($ICC_{2,1}$ =0.98 chest press; $ICC_{2,1}$=0.81 leg press) and demonstrated no systematic change when measured over 10 weeks in people with PWS.[23]

*Secondary outcome measures*

Muscle mass will be assessed using dual energy x-ray absorptiometry (DXA) whole body scans. DXA provides reliable data on body composition and is widely used in people with PWS.[1] Scans will be completed by a DXA licensed researcher who is blind to group allocation, according to manufacturer's instructions and on equipment calibrated daily. DXA scans will be carried out on the same equipment at each time point for each participant.

Functional strength will be assessed using four tests: sit-to-stand test,[29] weighted box-stacking test,[17] timed stair climb test[30] and 6-minute walk test.[31]

Physical activity will be assessed using Actigraph GT3X+ monitors (triaxial accelerometer) worn by participants on their waistbands for 7 consecutive days during waking hours. Participants will be considered adherent if they wear the monitor for at least 10 hours on at least 4 days including at least one weekend day.

Community participation (attendance or 'being there' and involvement or 'experience') will be assessed using three questionnaires completed by participants, or by parents or caregivers where necessary: the Adolescent Physical Activity Recall[32] questionnaire; the Adolescent Sedentary Activity[33] questionnaire; and, the community module of the Participation and Environment Measure-Children and Youth (PEM-CY).[34] The Adolescent Physical Activity Recall questionnaire has acceptable to good retest reliability (% agreement >70%; weighted kappa >0.5; ICC=0.3 to 0.9) across age, sex and seasons and evidence of construct validity (associated with aerobic fitness) in Australian adolescents aged 15 to 17 years.[32] The Adolescent Sedentary Activity questionnaire has good to excellent reliability (ICC=0.57 to 0.86) and good face validity in Australian adolescents aged 11 to 15 years.[33] The PEM-CY has evidence of good internal consistency for community participation frequency (ICC=0.70) and involvement (ICC=0.75), good retest reliability for community frequency (ICC=0.79) and involvement (ICC 0.69), and evidence of validity (significant effect of disability across variables) for children with disabilities aged 5 to 17 years.[35]

Health-related quality of life will be assessed using the Child Health Utility (CHU-9D)[36] instrument, a generic preference-based measure completed by the participants, and the parent-report Quality of Life Inventory-Disability (QI-Disability) questionnaire designed specifically for youth with complex disability.[37] The CHU-9D has evidence of criterion validity (Spearman's ρ=0.61) in Australian adolescents aged 11 to 17 years[38] and good retest reliability in children with inflammatory bowel disease aged 6 to 18 years (ICCs 0.71 to 0.89).[39] The QI-Disability questionnaire, developed for Australian children aged 5 to 18 years with intellectual disability across four diagnostic groups (Rett syndrome, Down syndrome, cerebral palsy or autism spectrum disorder), has evidence of convergent and discriminant validity (Cronbach's α of 0.72 to 0.90) and composite reliability (scores of 0.75 to 0.91).[40]

Behaviour will be assessed using the parent-report Developmental Behaviour Checklist,[41] which measures overall behavioural and emotional disturbance and 5 subscale scores (disruptive, self-absorbed, communication disturbance, anxiety, and social-relating disturbance).

Healthcare utilisation will be collected via a health service utilisation questionnaire developed for the trial. The questionnaire will collect data on hospital admissions and community allied health visits. Medicare Australia records will also be retrieved, with participant consent, to determine medical services and pharmaceutical use over one year.

*Other outcomes*

Demographic data on age, sex, medications (including growth hormone), co-morbidities, intellectual disability (parent/caregiver report or formal IQ testing scores if available) and social situation will be recorded at baseline. Anthropometric data on weight, height and waist circumference will be recorded at each assessment using a weighing scale, stadiometer and tape measure respectively, using standardised methods. Diet will be assessed using the online Australian Eating Survey (version 3) which is designed to measure typical food intake and is completed by the participant's parent or caregiver.

*Process evaluation*

Data on intervention fidelity and adverse events will be documented after each exercise session in an online exercise logbook (using REDCap software) by the exercise professional supervising the intervention.

Participant's experiences of exercising at a community gym setting will be explored by collecting qualitative data. Data on acceptability, benefits and social interactions with gym users during training will be documented from semi-structured interviews (conducted either in-person or via telephone or videoconference) with participants, their parent or caregiver and the exercise professional supervising the intervention (Table 2). Interviews will follow a question schedule and will be recorded and transcribed verbatim. Ideas that emerge in early interviews will be explored during later interviews to form a rich, nuanced understanding of the participant's experience. Photographs and short video recordings will also be collected by the exercise professional using an iPod (Apple Inc) provided, and shared with participants prior to the interview, to help stimulate conversations about the participant's experiences.[42, 43] Participants will be asked to talk about aspects of the program important to them and aspects they would consider changing. Brief observations on social interactions with other gym users during training will be documented in the exercise logbook by the supervising exercise professional.

**Table 2** Outcome measures

| Outcome | Measure | Description | Administration | Week 0 | Week 25 | Week 52 |
|---|---|---|---|---|---|---|
| ***PRIMARY*** | | | | | | |
| Muscle strength | 1RM chest press | Weight a participant can lift in a single seated chest press | Clinician observation | ✓ | ✓ | ✓ |
| | 1RM leg press | Weight a participant can lift in a single leg press | | | | |
| ***SECONDARY*** | | | | | | |
| Muscle mass | DXA whole body scan | Total lean mass, total fat mass, % body fat, regional lean mass, fat distribution | DXA licenced clinician | ✓ | ✓ | ✓ |
| Functional strength | Sit-to-stand | Time taken to stand up and sit down 5 times | Clinician observation | ✓ | ✓ | ✓ |
| | Weighted box stacking | Number of 10 kg boxes participants can lift in 1 min, from floor to a table 75 cm high | Clinician observation | ✓ | ✓ | ✓ |
| | Timed stairs climb | Time taken to ascend and descend a flight of stairs. Fastest time from 2 attempts | Clinician observation | ✓ | ✓ | ✓ |
| | 6-minute walk test | Distance walked in 6 mins over a 25 m course. Continuous encouragement allowed. | Clinician observation | ✓ | ✓ | ✓ |
| Physical activity | Daily total physical activity<br>Daily steps<br>Daily time sedentary | Daily total physical activity<br>Daily steps<br>Daily time spent sedentary | Tri-axial accelerometer worn on the waistband during waking hours for 7 days | ✓ | ✓ | ✓ |
| Community participation | Adolescent physical activity recall questionnaire | Type, duration and frequency of organised and non-organised physical activities done each week | Questionnaire, self-report or proxy-report | ✓ | ✓ | ✓ |
| | Adolescent sedentary activity questionnaire | 12-items, how often participants do sedentary activities on weekdays and weekends | Questionnaire, self-report or proxy-report | ✓ | ✓ | ✓ |
| | Community section of PEM-CY | 10 items, frequency and involvement of a participant in | Questionnaire, self-report or proxy-report | ✓ | ✓ | ✓ |

| | | | | | | |
|---|---|---|---|---|---|---|
| | | activities | | | | |
| Health-related quality of life | CHU-9D | 9-items, generic measure for young people | Questionnaire, self-report or proxy-report | ✓ | ✓ | ✓ |
| | QI-Disability | 42-items, specific measure for youth with complex disability | Questionnaire, proxy-report | | | |
| Behaviour | Developmental behaviour checklist | 96-items, 5 subscales | Online questionnaire, proxy-report | ✓ | ✓ | ✓ |
| Healthcare utilisation | Health utilisation questionnaire | Hospital admissions and community allied health visits (all cause) | Questionnaire, self-report or proxy-report | ✓ | ✓ | ✓ |
| | Medicare Australia data | Medical services, and pharmaceutical use over 12 months | Report Medicare Australia | | | ✓ |
| Diet | Australian Eating Survey | Food frequency questionnaire designed to measure typical food intake over 3 to 6 months | Online questionnaire, proxy-report | ✓ | ✓ | ✓ |
| ***PROCESS EVALUATION*** | | | | | | |
| Intervention fidelity | Adherence to trial protocol | Attendance, exercise type, intensity and volume, rest periods, and program frequency, duration and progression | Online exercise logbook completed by exercise professional | | ✓ | |
| Safety | Adverse events | Categorised as serious or non-serious, expected or unexpected, related or unrelated to the intervention | Online exercise logbook completed by exercise professional | | ✓ | |
| Gym experience | Participant experience | Exploring the experiences of people with PWS of exercising at a community gym | Semi-structured interviews with participants, their families and exercise professionals | | ✓ | |
| | | | Participant photographs and videos taken during training using iPod | | ✓ | |
| | Participant observation | Ethnographic methods | Researcher observation using ethnographic methods | | ✓ | |

Data about the participant's gym experiences will be complemented by an embedded qualitative observation study, using ethnographic methods, for a subgroup of up to 10 participants living in Victoria. A separate protocol for this embedded study will be reported elsewhere. Briefly, at least three training sessions, one during the initial, middle and final weeks of training, will be observed by a researcher. Overt observation will be used, where participants and exercise professionals are aware of a researcher's presence in the gym. Unstructured observations of the context, the interactions occurring between the person with PWS and other people in the gym and the reactions of others to the presence of the person with PWS will be documented in detail. Scratch notes at the time of observation will be made, from which detailed ethnographic field notes will be recorded that will provide an open-ended description of the exercise session, including events that occurred, reflections about the session, ideas for future observations, and thoughts comparing what was observed with other data reported. Data collection and analysis will occur in parallel, to allow ideas and reflections arising to be explored in subsequent observations.

## STATISTICAL ANALYSIS

*Sample size estimation*

Our pilot trial found moderate to large increases (effect sizes 0.78 and 0.92) for upper and lower limb strength after 10 weeks of progressive resistance training in young people with PWS. Assuming an effect size of 0.78, equating to improvement in strength of 15-25%, is clinically significant, two-sided 5% significance level and a power of 80%, a sample size of 27 participants per group (total 54) is necessary. Allowing for a conservative 10% dropout rate (given no dropouts in the pilot trial), we aim to recruit 60 participants.

*Analysis of quantitative outcomes*

Data will be analysed according to intention to treat principles using linear mixed effects models for primary outcomes, with treatment group as a covariate. Modelling will account for variation in baseline values, for within-participant dependence of observations taken over time, and for missing data, allowing some participants to have missing observations at certain time points. Random effects will be used for individuals to account for correlated repeated measures and for site. Visualisation of residuals will be used to look for model assumption errors, and transformations will be used if needed. If outliers are present, a robust linear mixed effects analysis will also be fitted as a sensitivity analysis. If more than 5% of data are missing, a multiple imputation process will be used, providing the assumption data are missing at random is met and where covariates related to missingness will be used to generate the imputed data. If multiple imputation is required, the results will be used as a sensitivity analysis to compare with the main analysis to check for any potential biases related to missingness. A similar approach will be used for analysis of quantitative secondary outcomes. Process evaluation will assess intervention fidelity (including confirming progression in resistance during training over 24 weeks and if ceiling effects are observed) and will explore causal mechanisms of impact (using mediation analysis[44]) including whether improvements in muscle strength are mediated by changes in muscle mass and other factors associated with variation in outcomes.[45] The CONSORT 2010[46] and the consensus on exercise reporting template (CERT)[47] guidelines will guide reporting.

*Analysis of qualitative outcomes*

The theoretical framework underpinning the qualitative data analysis is interpretive description.[48] Interpretative description seeks to understand experiences in a way that can be meaningfully applied to clinical practice. It was chosen because a focus of this trial is to

establish new knowledge of pragmatic strategies that could support successful implementation of exercise programs for people with PWS rather than creating new theory. The Consolidated criteria for Reporting Qualitative research (COREQ) checklist[49] will guide reporting.

Computer software (NVivo; QSR International, Melbourne) will be used to manage the qualitative data analysis of participant interviews. Initial analysis will involve two researchers independently coding transcripts line-by-line. Next, the researchers will meet to review codes and to group emergent codes into categories, subthemes and themes using inductive reasoning. Strategies to ensure credibility, transferability and dependability will include triangulation with quantitative data, exercise logs, and observation data; and using 'rich thick description', whereby verbatim quotations are included to exemplify themes.[50] Member checking will be completed to provide the opportunity for participants to confirm transcripts reflect their thoughts, and to verify interpretation of the data after initial analysis.

*Health economic analysis*

The health economic analysis will evaluate cost-effectiveness from healthcare and societal perspectives, with outcomes based on the primary intermediate clinical outcome (15% difference in leg muscle strength) and the secondary outcome of health-related quality of life (CHU-9D). The control group are an attention placebo-control; as such the "sham" intervention delivered has no bearing to "usual care". In line with other placebo-control trials, there will be no delivery costs attributed to this group. Program costs associated with the intervention will be attributed to the experimental group only. These will be determined from a register of staff and the time engaged in the supervision of participant training. Labour costs will be attributed to the staff member to determine an intervention cost per experimental group participant. In addition, mean fixed costs associated with training and any other fixed intervention costs will be attributed to experimental group participants. Total costs for each participant will be determined from the intervention costs and cost of self-reported health services and Medicare Services Australia (primary care visits and prescription pharmaceuticals) utilised following completion of the intervention for both groups up to week-52. The incremental cost effectiveness ratio (ICER) around the primary outcome will be calculated as the difference in total program and health service costs between the groups over one year. A cost utility ratio will be calculated based on the secondary outcome measure as the change in total program and health service cost per change in quality adjusted life years saved in the experimental and control groups over one year. One-way sensitivity analyses will investigate robustness of the cost effectiveness ratio to a range of cost and effect estimates. On the cost side, this may include alternative delivery arrangements, including scaling up the intervention, wage rates and program length; on the effect side health-related quality of life and muscle strength. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) will guide reporting.[51]

**Patient and Public Involvement**

This proposal was co-developed in consultation with partner organisations (Prader-Willi Syndrome Association of Australia; Prader-Willi Research Foundation of Australia) and parents of people with PWS. The trial governance structure comprises a project steering committee and a data monitoring committee. The project steering committee will monitor trial implementation and performance, oversee and manage the budget, provide strategic support and specialist advice, identify and manage risks and agreed standard operating procedures. The committee membership will comprise researchers (all chief investigators),

clinicians (all associate investigators) and at least two consumer representatives from the PWS community. The steering committee meets bi-monthly by videoconference and will meet face-to-face as required. The data monitoring committee will meet at least once a year to monitor safety and data quality and will review any adverse events that occur. This committee will comprise a chair from the research team and two expert clinicians from participating sites.

## ETHICS AND DISSEMINATION

Ethical approval was granted by Royal Children's Hospital, Melbourne through the National Mutual Acceptance initiative as participants will be recruited throughout Australia. Research governance approval was obtained from five sites (Royal Children's Hospital, Melbourne; Austin Hospital, Melbourne; Royal Prince Alfred Hospital, Sydney; Queensland Children's Hospital, Brisbane; Princess Alexandra Hospital, Brisbane). Ethics approval was registered with relevant universities. Any modifications to the protocol will be submitted for ethics approval and noted on the trial registration.

Young adults with PWS (18 and over) will provide their own written informed consent to participate where they provide their own consent in usual practice. For adults who do not normally provide their own consent, their legal guardian will provide written informed consent on their behalf, consistent with the relevant Act covering medical decision making in the jurisdiction.[52] In this case, the adult with PWS is also invited to provide their own written consent (online supplemental appendix 2). For adolescents with PWS (13 to 17 years), written informed consent will be obtained from their parents or guardians. Adolescents with PWS are also invited to provide their own written consent based on their parents' recommendation for whether this is appropriate. Allocation is concealed at the time of consent and consent will be obtained by the trial coordinator. Separate consent will also be sought to access participant data from the Medicare Benefits Scheme and Pharmaceutical Benefits Scheme.

Participant confidentiality is strictly held in trust by the investigators, research staff, and the sponsoring institution. All identifiable participant data, including clinical data, will be held in strict confidence and will not be released to any unauthorised third party without written permission of the participant, except as necessary for monitoring by the ethics committee or regulatory agencies.

Our procedure for adverse events is for these to be recorded during the intervention period until resolution or stabilisation, regardless of their relationship to the intervention. The exercise professional supervising the training is responsible for recording in the participant's exercise logbook the date, actions taken. and outcome of the adverse event; and for the Principal Investigator to subsequently record the expectedness, severity, seriousness and association to the intervention, based on temporal relationship and clinical judgment. The exercise professional will report all serious adverse events within 24 hours to the Principal Investigator, who will then submit a report to the approving Human Research Ethics Committee and to the relevant research governance offices without undue delay and no later than 15 calendar days. The report will clarify the impact of the event on participant safety, trial conduct and trial documentation. La Trobe University has clinical trial insurance in place in case of serious adverse events occurring during this trial.

Given the dearth of literature to support the design and delivery of exercise programs for people with cognitive disability and behavioural challenges, a knowledge translation plan guided by the Practical Robust Implementation and Sustainability Model[53] to support adoption and implementation of strategies and processes for people with PWS is incorporated within this trial. We aim to meet the needs of people with PWS, their families and the health and recreation sectors by (1) planning for sustainability through the development of free resources to assist implementation of exercise programs for people with PWS by exercise professionals, community exercise venues, and other local health agencies; (2) sharing best practice by gathering exemplars of implementation; (3) facilitating access to exercise opportunities by working with parents, caregivers and others (e.g. residential care facility staff) on how community exercise programs articulate with available disability funding and mapping implementation costs; (4) training those who work with people with PWS through professional development seminars; and, (5) disseminating outcomes broadly to people with PWS and their families (e.g. newsletters, blogs, social media, public talks) and health professionals (e.g. publications, presentations). The contribution of the participants with PWS will be directly acknowledged. Consistent with Australian National Health and Medical Research Council policies, de-identified data from the trial will be made available through OPAL, La Trobe University's Institutional Repository or through online supplemental data files accompanying publication of findings.

## DISCUSSION

The outcomes of this trial have the potential to improve the clinical management of people with PWS. Strength training is not part of usual clinical care for people with PWS and if found to be effective, it would be a good exercise choice as the required skills can usually be mastered by people with intellectual disabilities.[54] Muscle weakness, low muscle tone and poor motor proficiency can reduce the desire of people with PWS to be physically active. This in turn reduces their participation in exercise,[14] leading to a cycle of sedentary behaviour, deteriorating muscle function, obesity, greater metabolic risk, social isolation, lower quality of life,[15] and early mortality.[55] Therefore, facilitating adequate muscle strength could help break the cycle of sedentary behaviour and encouraging healthy lifestyle behaviours.

This trial is designed to help meet the needs of people with PWS, their families and the broader health community. Exercise program availability with one-on-one support emerged as a major theme in a survey of the needs of 105 families with a child or youth with PWS.[13] This trial will provide high-level evidence of how to effectively implement exercise in local community-settings for people with PWS. Their complex behavioural issues are a substantial threat to exercise adherence, and so it is important to determine what pragmatic strategies support community-based exercise participation for people with PWS. Integrated knowledge translation plans are a vital part of all randomised controlled trials to address the disconnect between research and practice.[56] There is limited literature available to support the design and delivery of exercise programs for people with intellectual disability. Our knowledge translation plan includes broad dissemination of our outputs to health and community groups to address this implementation knowledge gap. Future research could investigate the potential for similar active recreation initiatives to reduce health inequality and poor health outcomes by increasing inclusion in community exercise for people with complex disabilities such as PWS.

There is a dearth of clinical trials involving adults with intellectual disability.[57] A strength of this research is that when completed it will be the largest efficacy trial of an exercise intervention for people with PWS. By incorporating a health economic evaluation, it will also provide high-level evidence of whether strength training is a cost-effective intervention for people with PWS. This is important as people with PWS and their families need high-quality evidence to support them to make evidence-informed healthcare decisions. The combination of robust clinical and economic data will also provide high-quality evidence to inform health and disability policy decisions. A limitation of this trial is the paucity of outcome measures to assess participation and health-related quality of life outcomes for adolescents and adults with PWS. While the measures selected were designed for adolescents up to the age of 17 years, these measures have been implemented with young adults with disability up to the age of 30 years in a previous trial.[58] A further limitation is that although participants and assessors will be blinded to group allocation, it is not possible to blind exercise professionals.

This randomised controlled trial will determine the efficacy and cost-effectiveness of community-based progressive resistance training for people with PWS. By incorporating embedded health economic evaluation and qualitative analysis of exercise participation experiences, it will provide robust clinical and health economic data to inform policy and practice.

**Authors' contributions:** NS led the research team in the conception, design and coordination of this trial, acquisition of funding and the drafting and critical revision of the manuscript. KB, LR, TM, CB, NT contributed as chief investigators to the trial design, acquisition of funding, in ongoing monitoring of trial progress, and critically reviewed the manuscript. AS contributed substantially as the trial coordinator and the revision of the manuscript. LP contributed to the trial design (sample size estimation and data analysis plan), acquisition of funding, is involved in the ongoing monitoring of trial progress and critically reviewed this manuscript. JW contributed to the study design (economic evaluation component), acquisition of funding, project steering committees and critical revision of this manuscript. CS contributed as a PhD student (qualitative data collection and analysis) and to revision of the manuscript. VC, JF, DL, GL, ZM, JP, SB contributed as associate investigators (clinical expertise) contributing to trial design, acquisition of funding and critical revision of this manuscript. SB contributed substantially as a consumer representative to the development of trial resources and processes and to the revision of the manuscript. All authors read and approved the final manuscript.

**Competing interests statement:** None declared.

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**Data sharing statement:** Individual participant data for published primary and secondary quantitative outcome measures will be made available via open access (university library repository) following the publication of the main trial outcomes.

**Trial status:** Enrolment for the trial began in February 2020 and the final participant was randomised in September 2022. Data collection will continue until September 2023.

**Ethics approval**: Ethics approval was obtained from Royal Children's Hospital, Melbourne HREC/50874/RCHM-2019 under the National Mutual Acceptance initiative. Ethics approval has been registered with La Trobe University, the University of Melbourne and Deakin University.

**Trial personnel:** The PRESTO trial research team comprises:

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## FIGURE LEGEND

**Figure 1** Trial Design

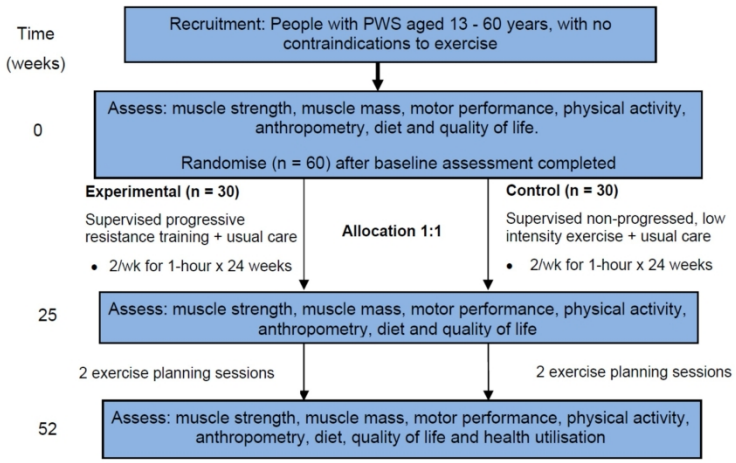


Figure 1 Trial design

209x297mm (300 x 300 DPI)

# Trial Review

COVID-19 studies are our top priority.

For new and updated trial submissions, we are processing trials as quickly as possible and appreciate your patience. We recommend submitting your trial for registration at the same time as ethics submission.

VIEW TRIAL AT REGISTRATION VIEW HISTORY

The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been endorsed by the ANZCTR. Before participating in a study, talk to your health care provider and refer to this information for consumers

< BACK

## Trial registered on ANZCTR

| | |
|---|---|
| **Registration number** | ACTRN12620000416998 |
| **Ethics application status** | Approved |
| **Date submitted** | 12/03/2020 |
| **Date registered** | 27/03/2020 |
| **Date last updated** | 21/10/2021 |
| **Date data sharing statement initially provided** | 27/03/2020 |
| **Type of registration** | Prospectively registered |

### Titles & IDs

| | |
|---|---|
| **Public title** | Improving muscle strength in young people with Prader-Willi syndrome: a phase II randomised trial |
| **Scientific title** | The effect of exercise on muscle strength in young people with Prader-Willi syndrome: a phase II randomised trial |
| **Secondary ID [1]** | None |
| **Universal Trial Number (UTN)** | |
| **Trial acronym** | PRESTO |
| **Linked study record** | |

### Health condition

**Health condition(s) or problem(s) studied:**

Prader-Willi syndrome

| **Condition category** | **Condition code** |
|---|---|
| Human Genetics and Inherited Disorders | Other human genetics and inherited disorders |

### Intervention/exposure

| | |
|---|---|
| **Study type** | Interventional |
| **Description of intervention(s) / exposure** | Participants will be randomised to receive one of two exercises programs.<br>Intervention group participants will complete an exercise program, supervised 1:1 by an exercise professional.<br>Participants will exercise twice a week for 24 weeks (48 sessions in total). Each exercise session will last |

| | |
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| | approximately 60 minutes.<br>All exercise sessions will take place in a community gym local to the participant.<br>The exercise program will be supervised by an exercise professional (usually a physiotherapist, exercise physiologist or personal trainer). Exercise professionals will be invited to participate based on their location and typical practice (e.g. working in paediatrics, neurological, or musculoskeletal areas). They will receive a training manual that includes details about the trial protocol, specialist advice on Prader-Willi syndrome, how to facilitate exercise in people with Prader-Willi syndrome, communication strategies, and behaviour management.<br>The exercise professional will complete an exercise log (either in hard copy or online) on behalf of the participant to document the exercises completed and any adverse events that occur.<br>Participants will also receive 2 planning sessions of 1-hour duration following the intervention period with a facilitator to encourage their ongoing participation in community exercise. These sessions will be conducted by an exercise professional either in person or via videoconference. The content of these sessions will be individualised and will aim to address barriers to taking part in ongoing community exercise. These sessions will take place approximately 1 month and 3 months after the end of the intervention. |
| **Intervention code [1]** | Rehabilitation |
| **Comparator / control treatment** | Control group participants will also complete an exercise program, supervised 1:1 by an exercise professional.<br>Participants will exercise twice a week for 24 weeks (48 sessions in total). Each exercise session will last approximately 60 mins,<br>All exercise sessions will take place in a community gym local to the participant.<br>The exercise program will be supervised by an exercise professional (usually a physiotherapist, exercise physiologist or personal trainer).<br>Exercise professionals will be invited to participate based on their location and typical practice (e.g. working in paediatrics, neurological, or musculoskeletal areas). They will receive a training manual that includes details about the trial protocol, specialist advice on Prader-Willi syndrome, how to facilitate exercise in people with Prader-Willi syndrome, communication strategies, and behaviour management,<br>The exercise professional will complete an exercise log (either in hard copy of online) on behalf of the participant to document the exercises completed and any adverse events that occur.<br>Participants will also received 2 planning sessions of 1-hour duration following the intervention period with a facilitator to encourage their ongoing participation in community exercise. These sessions will be conducted by an exercise professional either in person or via videoconference. The content of these sessions will be individualised and will aim to address barriers to taking part in ongoing community exercise. These sessions will take place approximately 1 month and 3 months after the end of the intervention. |
| **Control group** | Active |

## Outcomes

| | |
|---|---|
| **Primary outcome [1]** | Muscle strength- of the arms and legs will be assessed using 1 repetition maximum (1RM) force generation tests. Composite measures of arm (chest press) and leg (leg press) strength will establish the amount of weight each participant can lift once. |
| ***Timepoint [1]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [1]** | Lean muscle mass will be assessed using a dual energy x-ray absorptiometry (DXA) whole body scan for total lean (muscle) mass and regional lean mass. DXA scans will be carried out on the same equipment at each time point for each participant at each site. |
| ***Timepoint [1]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [2]** | Sit-to-stand test: measures how long it takes to stand up and sit down 5 times |
| ***Timepoint [2]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [3]** | Weighted box-stacking test: measures how many boxes weighing 10kg can be stacked in one minute |
| ***Timepoint [3]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [4]** | Timed stair climb test: measures how long it takes to go up and down a standard flight of stairs |
| ***Timepoint [4]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [5]** | 6-minute walk test: measures distance walked by the participant in 6 minutes |
| ***Timepoint [5]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [6]** | Physical activity levels (accelerometry): Actigraph GT3X+ accelerometers will be used to measure total physical activity, total sedentary time and the number of steps participants take during waking hours over 7 consecutive days. |
| ***Timepoint [6]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [7]** | Community participation (attendance): will be measured using the Adolescent Physical Activity Recall, the Adolescent Sedentary Activity, and the community section of the Participation and Environment Measure-Children and Youth questionnaires. These questionnaires measure what sports and other physical activities the participant does, how often and for how long and will be completed by participants and/or their family member or residential caregivers where necessary. |
| ***Timepoint [7]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [8]** | Community participation (involvement): will be measured using the community section of the Participation |

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| | and Environment Measure-Children and Youth questionnaire. This questionnaire measures how involved participants feel in 10 activities and will be completed by participants and/or their family member or residential caregivers where necessary. |
| ***Timepoint [8]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [9]** | Health related quality of life: will be measured using the 9-item Child Health Utility (CHU-9D) instrument and the Quality of Life Inventory-Disability questionnaire. The CHU-9D will be completed by participants and/or their family members or residential caregivers where necessary. The Quality of Life Inventory-Disability questionnaire will be completed by family members or caregivers. |
| ***Timepoint [9]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [10]** | Healthcare utilisation: will be assessed via a health service utilisation questionnaire developed for the trial and completed by participants and/or their family members or residential caregivers where necessary. The questionnaire will collect data on hospital admissions and community allied health visits. |
| ***Timepoint [10]*** | Week O (baseline, week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [11]** | Adverse events: will be categorised as serious or non-serious, expected or unexpected, and related or unrelated to the trial will be documented in the participant's exercise logbook completed by the health professional (usually a physiotherapist) supervising the intervention. Examples of possible adverse events are delayed onset muscle soreness, increased anxiety resulting in skin picking or a temper outburst (behavioural features of Prader-Willi syndrome) and food stealing. |
| ***Timepoint [11]*** | During intervention phase of the trial (compiled at week 25, immediately post intervention) |
| **Secondary outcome [12]** | Diet: will be documented by parents and carers (not participants) using the online version of the Australian Eating Survey |
| ***Timepoint [12]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [13]** | Gym experience: qualitative data about the participants' experience of exercise will be collected from both groups (intervention and control). Data on acceptability, benefits and social interactions with gym users during training will be documented from semi-structured interviews with participants and their families. Photographs and video diaries will also be collected by participants using an iPod touch given to them on loan by the research team at trial commencement. Data on social interactions with other gym users will be documented in the participant's exercise log during training by the health professional delivering the intervention. Data collection will be supplemented by observation (using ethnographic methods) for a subgroup of participants (n=10 participants), where 3 training sessions (one session during initial weeks, middle weeks and final weeks of training) will be observed. |
| ***Timepoint [13]*** | During intervention phase of the trial (compiled at week 25, immediately post intervention) |
| **Secondary outcome [14]** | Behaviour will be measured using the Developmental Behaviour Checklist questionnaire. The Developmental Behaviour Checklist -Parent version (DBC-P) will be completed by family members or residential caregivers of adolescents (aged 13-17 years) and the Developmental Behaviour Checklist -Adult version (DBC-A) will be completed by family members or residential caregivers of adults (aged 18 years and over). |
| ***Timepoint [14]*** | Week 0 (baseline), week 25 (immediately post intervention) and week 52 (6-months post intervention) |
| **Secondary outcome [15]** | Medicare Australia records will be retrieved with participant consent to determine medical services and pharmaceutical use over 12 months. |
| ***Timepoint [15]*** | Week 52 (6-months post-intervention) |

## Eligibility

| | |
|---|---|
| **Key inclusion criteria** | Each participant must meet all of the following criteria to be enrolled in this trial:<br>• Have genetically confirmed Prader-Willi syndrome,<br>• Aged between 13 and 60 years (inclusive) at the time of randomisation,<br>• Able to follow simple verbal instructions in English,<br>• Medical clearance from their general practitioners or physician certifying they can participate (where considered necessary based on answers to the pre-exercise screening questionnaire PAR-Q+),<br>• Provide a signed and dated informed consent form or has a legally acceptable representative capable of understanding the informed consent document and providing consent on the participant's behalf. |
| **Minimum age** | 13 Years |
| **Maximum age** | 60 Years |
| **Gender** | Both males and females |
| **Can healthy volunteers participate?** | No |
| **Key exclusion criteria** | People meeting any of the following criteria will be excluded from the trial:<br>• Has participated in progressive resistance training in the 3 months prior to randomisation<br>• Has a concurrent physical (e.g. severe arthritis), psychological (e.g. severe psychosis) or behavioural issue (e.g. violent behaviour) that might affect their ability to participate in a 24-week exercise program.<br>• Inability or unwillingness of participant or legally acceptable representative to give written informed consent. |

## Study design

| | |
|---|---|
| **Purpose of the study** | Treatment |
| **Allocation to intervention** | Randomised controlled trial |
| **Procedure for enrolling a subject and allocating the treatment (allocation concealment procedures)** | |
| **Methods used to generate the sequence in which subjects will be randomised (sequence generation)** | |
| **Masking / blinding** | Blinded (masking used) |
| **Who is / are masked / blinded?** | The people receiving the treatment/s<br><br>The people assessing the outcomes<br>The people analysing the results/data |
| **Intervention assignment** | Parallel |
| **Other design features** | |
| **Phase** | Not Applicable |
| **Type of endpoint(s)** | |
| **Statistical methods / analysis** | |

## Recruitment

| | |
|---|---|
| **Recruitment status** | Recruiting |

**Date of first participant enrolment**

| | | | |
|---|---|---|---|
| **Anticipated** | 3/04/2020 | **Actual** | 24/02/2021 |

**Date of last participant enrolment**

| | | | |
|---|---|---|---|
| **Anticipated** | | **Actual** | |

**Date of last data collection**

| | | | |
|---|---|---|---|
| **Anticipated** | | **Actual** | |

**Sample size**

| | | | | | |
|---|---|---|---|---|---|
| **Target** | 60 | **Accrual to date** | 24 | **Final** | |

**Recruitment in Australia**

| | |
|---|---|
| **Recruitment state(s)** | NSW,QLD,VIC |
| **Recruitment hospital [1]** | The Royal Childrens Hospital - Parkville |
| **Recruitment hospital [2]** | Royal Prince Alfred Hospital - Camperdown |
| **Recruitment hospital [3]** | Princess Alexandra Hospital - Woolloongabba |
| **Recruitment hospital [4]** | Queensland Children's Hospital - South Brisbane |
| **Recruitment hospital [5]** | Austin Health - Austin Hospital - Heidelberg |
| **Recruitment postcode(s) [1]** | 3052 - Parkville |
| **Recruitment postcode(s) [2]** | 2050 - Camperdown |
| **Recruitment postcode(s) [3]** | 4102 - Woolloongabba |
| **Recruitment postcode(s) [4]** | 4101 - South Brisbane |
| **Recruitment postcode(s) [5]** | 3084 - Heidelberg |

## Funding & Sponsors

| | |
|---|---|
| **Funding source category [1]** | Government body |
| **Name [1]** | Medical Research Future Fund |
| **Address [1]** | Department of Health<br>GPO Box 9848<br>Canberra ACT 2601<br>Australia |
| **Country [1]** | Australia |
| **Primary sponsor type** | University |
| **Name** | La Trobe University |

| | |
|---|---|
| **Address** | Kingsbury Drive,<br>Bundoora,<br>VIC 3086 |
| **Country** | Australia |
| **Secondary sponsor category [1]** | None |
| **Name [1]** | |
| **Address [1]** | |
| **Country [1]** | |

## Ethics approval

| | |
|---|---|
| **Ethics application status** | Approved |
| **Ethics committee name [1]** | The Royal Children's Hospital Melbourne Human Research Ethics Committee |
| **Ethics committee address [1]** | 50 Flemington Rd,<br>Parkville<br>VIC 3052 |
| **Ethics committee country [1]** | Australia |
| **Date submitted for ethics approval [1]** | |
| **Approval date [1]** | 18/04/2019 |
| **Ethics approval number [1]** | 2019.048 |

## Summary

| | |
|---|---|
| **Brief summary** | We will investigate if exercise is effective in increasing muscle strength in people with Prader-Willi syndrome (PWS). We will conduct a phase II, multi-site, double-blind, randomised controlled trial with 6-month follow-up. Sixty participants with PWS aged 13 to 60 years will be randomised to receive one of two exercise programs. Participants will exercise twice a week for 24 weeks at their local gym supervised by an exercise health professional (usually a physiotherapist). We will measure muscle strength, muscle mass, functional strength, physical activity, community participation, and health-related quality of life at baseline (week 0), after the intervention (week 25) and 6 months later (week 52): We will recruit participants through PWS advocacy groups, specialist PWS clinics, and PWS registries and clinical databases. |
| **Trial website** | |
| **Trial related presentations / publications** | |
| **Public notes** | |

## Contacts

### Principal investigator

| | |
|---|---|
| **Name** | Prof Nora Shields |
| **Address** | Department of Physiotherapy, Podiatry, Prosthetics and Orthotics,<br>La Trobe University,<br>VIC 3086 |
| **Country** | Australia |
| **Phone** | +61 3 9479 5852 |
| Fax | |
| **Email** | n.shields@latrobe.edu.au |

### Contact person for public queries

| | |
|---|---|
| **Name** | Prof Nora Shields |
| **Address** | Department of Physiotherapy, Podiatry, Prosthetics and Orthotics,<br>La Trobe University,<br>VIC 3086 |
| **Country** | Australia |
| **Phone** | +61 3 9479 5852 |
| Fax | |
| **Email** | n.shields@latrobe.edu.au |

### Contact person for scientific queries

| | |
|---|---|
| **Name** | Prof Nora Shields |

| | |
|---|---|
| **Address** | Department of Physiotherapy, Podiatry, Prosthetics and Orthotics,<br>La Trobe University,<br>VIC 3086 |
| **Country** | Australia |
| **Phone** | +61 3 9479 5852 |
| Fax | |
| **Email** | n.shields@latrobe.edu.au |


## Data sharing statement

| | |
|---|---|
| **Will individual participant data (IPD) for this trial be available (including data dictionaries)?** | Yes |
| **What data in particular will be shared?** | Individual participant data for published primary and secondary quantitative outcome measures. |
| **When will data be available (start and end dates)?** | Following the publication of the main trial outcomes (circa 2024), no end date. |
| **Available to whom?** | Data will be open access. |
| **Available for what types of analyses?** | Data will be available for any purpose including meta-analyses. |
| **How or where can data be obtained?** | Data will be deposited in the La Trobe University library repository. |
| **What supporting documents are/will be available?** | Study protocol<br>Ethical approval |

## How or where can supporting documents be obtained?

| | |
|---|---|
| Type [1] | Ethical approval |
| Citation [1] | |
| Link [1] | |
| Email [1] | |
| Other [1] | |
| Attachment [1] | /Steps11and12/377484-(Uploaded-08-07-2019-12-31-15)-Study-related document.pdf |
| Type [2] | Study protocol |
| Citation [2] | |
| Link [2] | |
| Email [2] | |
| Other [2] | We aim to publish a study protocol in an open access journal. |
| Attachment [2] | |

## Summary results

No Results

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# Participant Information Sheet/Consent Form – Parent/Guardian

**Interventional Study** - *Parent/Guardian consenting on behalf of participant*

| | |
|---|---|
| **Title:** | Improving muscle strength in young people with Prader-Willi syndrome: a phase II randomised trial |
| **Short Title** | Exercise for people with Prader-Willi syndrome (PRESTO trial) |
| **Project Sponsor** | La Trobe University |
| **Principal Investigator** | Prof Nora Shields |
| **Associate Investigator(s)** | Prof Kim Bennell<br>Prof Nicholas Taylor<br>Dr Lauren Rice<br>A/Prof Tania Markovic<br>Prof Chris Bigby<br>A/Prof Jenny Watts<br>A/Prof Luke Prendergast |

## Part 1 What does the young person's participation involve?

### 1 Introduction

This is an invitation for the young person in your care to take part in this research project. The young person is being invited to take part because they have Prader-Willi syndrome. In this project we want to find out if it would be helpful for young people with Prader-Willi syndrome to do exercise.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want the young person to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not the adolescent or young adult can take part, you might want to talk about it with a relative, friend or the adolescent or young adult's local doctor.

### 2 Do I have to take part in this research project?

**Participation is voluntary**
The young person's participation in this study is completely voluntary and there will be no cost to you or the young person. If you do not want the young person to take part in this study they do not have to. They should feel under no obligation to participate in this study. Choosing not to take part in this study will not affect their current and future medical care in any way.

If you decide you want the young person to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
• Understand what you have read
• Consent to the young person taking part in the research project

• Consent for the young person to have the tests and treatments that are described
• Consent to the use of the young person's personal and health information as described, including the young person's Medicare Benefits Schedule (MBS) and/or Pharmaceutical Benefits Scheme (PBS) data.

**Your withdrawal from the study**
The young person is under no obligation to continue with the research study. They may change their mind at any time about participating in the research. People withdraw from studies for various reasons and they do not need to provide a reason.

You can withdraw the young person from the study at any time by completing and signing the **'Form for Withdrawal of Participation – Parent/Guardian'**. This form is provided at the end of this document and is to be completed by you and supplied to the research team if you choose to withdraw the young person at a later date.

If you withdraw the young person from the study, you will be able to choose whether the researchers will destroy or retain the information they have collected about the young person. You should only choose **one** of these options. Where both boxes are ticked in error or neither box is ticked, the study will destroy all MBS and PBS information it has collected about the young person.

You will be given a copy of this Participant Information and Consent Form to keep.

## 3 What is the purpose of this research?

In this study we want to find out if doing exercise for 6 months at a community gym is good for young people with Prader Willi syndrome aged 13 years and over.

Exercise is considered an important part of the treatment of Prader-Willi syndrome. However, very little is known about what type of exercise is best for people with Prader-Willi syndrome. We also don't know much about what helps people with Prader-Willi syndrome to exercise. This project will help us understand what type of exercise is good for people with Prader-Willi syndrome and how to support people with Prader-Willi syndrome to exercise in their community.

## 4 What does participation in this research involve?

The young person will be taking part in a project called a double-blind, randomised controlled research project. This means we will put the young person into one of two groups, but they will not know which group they are in. The young person will be put into a group by chance. They have a 50/50 chance of being in each group.

Each group will get a different exercise program. Both groups will exercise at a community gym. Both groups will be supervised by an exercise professional, who will usually be a physiotherapist or a personal trainer. Both groups will exercise twice a week for 24 weeks. The researchers will know which exercise program the young person is getting. We will compare the results of the groups to see which exercise program is better.

### *(i) What does the exercise program involve?*

The young person will be asked to do an exercise program for 24 weeks. The young person will exercise 2 times each week for about 1 hour. The young person will do the exercise program at a community gym. The gym will be close to where the young person lives.

The young person will also receive 2 exercise planning sessions after their exercise program. The young person will do one planning session 1 month after they finish their exercise program and one planning session 3 months after they finish their exercise program. Each session will go for about 1 hour.

An exercise professional will help the young person to do the exercise program. The health professional will probably be a physiotherapist or a personal trainer. This person will write down things about the young person's exercise program in a diary or iPod. They will write down things like:

- how many exercise sessions the young person did,
- what exercises the young person did,
- if there were any problems with exercising,
- if the young person talked to other people at the gym

We will give the exercise professional an iPod at the start of the exercise program. The exercise professional will assist the young person to use the iPod to take photographs to tell us about the exercise program. The young person might take photographs of things they like or dislike about the exercise program. The young person will be asked to record short videos to tell short stories about things that happened at the gym. The young person will use these photographs and videos to help them tell their story to the researcher during an interview with one of the researchers. This interview will take place after the young person finishes the exercise program. The interview can be done face-to-face, by telephone or by videoconference. In the interview the young person will talk about their experiences exercising at the gym. The interview will take about 20 minutes. We will record the interview so we can listen to the answers later. The young person can ask to end the interview at any time.

You will also be invited to do an interview with one of the researchers. You will be asked to talk about what you think about the young person doing an exercise program at the gym. The young person can choose if they would like to do the interviews separately or together with you.

If the young person lives in Victoria, they may have a researcher come and watch between three and five of the exercise sessions. The researcher will make notes to describe what happened during the exercise session, such as who was in the gym, and if the young person spoke with other people at the gym.

***(ii) What tests will we be asked to do?***

The young person will need to do some tests if they take part in this project. The young person will do these tests before the start the exercise program, at the end of the exercise program and 6 months after the exercise program.

The young person will be asked to do the following tests at each testing visit:

| | Test | How we do the test |
|---|---|---|
| **1** | *Muscle strength* | Measures how much weight the young person can lift or push with their arms and legs |
| **2** | *Muscle size* | A whole body scan called a DXA scan will be done. A DXA scan is a type of x-ray. The young person will need to lie down on the machine that does the scan. They will need to be still for about 15 minutes while the scan is being done. The scan measures the size of their muscles. Their waist circumference, weight and height will be measured before this test. |
| **3** | *Timed stairs test* | Measures how long it takes the young person to go up and down a flight of stairs |
| **4** | *Box stacking* | Measures how many boxes the young person can stack in one minute |
| **5** | *Sit to stand test* | Measures how long it takes the young person to stand up and sit down 5 times |
| **6** | *6-minute walk* | Measures how far the young person can walk in 6 minutes |

| | | |
|---|---|---|
| **7** | *Physical activity* | The young person will be asked to wear a small monitor for 8 days on their waist to measure the amount of movement they do. |
| **8** | *Physical activity recall questionnaire* | Asks questions about what sports, games and other physical activities the young person does, how many times a week the young person does these activities and how long the young person spends doing these activities.<br>You may help the young person answer the questions. |
| **9** | *Sedentary activity questionnaire* | Asks questions about 12 sedentary activities the young person might do and how often they do them during the week and at the weekends.<br>You can help you the young person answer the questions. |
| **10** | *Participation and environment measure (community section)* | Asks questions about 10 community activities the young person might do and how involved they are in those activities. There are also questions about the young person's community, and what makes it easier or harder for them to take part in the community.<br>You can help the young person answer the questions. |
| **11** | *Child Health Utility questionnaire* | Asks 9 questions about the young person's quality of life. The young person will answer the questions on this form themselves if they can.<br>You can help the young person answer the questions if they have difficulty answering themselves. |
| **12** | *Quality of life Inventory- Disability questionnaire* | Asks 42 questions about the young person's quality of life.<br>This form is answered by you. |
| **13** | *Developmental behaviour checklist* | Asks 96 questions about your behaviour.<br>This form is answered by you. |
| **14** | *Health utilisation* | We want to find out if the exercise program is value for money. To do this we will collect information about the young person and their family such as where they work or go to school, how much money they earn, what help they need from other people, how much it costs them to do the exercise program and how often they see a health professional such as your GP or physiotherapist.<br>This form is answered by you. |
| **15** | *Diet* | You will be asked to fill in a survey about the young person's diet. It will take about 15 minutes. |

***(iii) Where will the tests be done? How long will the testing session take?***

We will do the testing sessions at:

- La Trobe University, Melbourne campus in Bundoora, in Melbourne, Victoria;
- CPC RPA Clinic, Boden Institute, Charles Perkins Centre at the University of Sydney in Camperdown, in Sydney, New South Wales
- Princess Alexandra Hospital, in Brisbane, Queensland.

When there are circumstances that mean a young person cannot travel to one of the above assessment sites, we will organise for the assessments to be done as close as possible to where the young person lives.

Each testing session will take about 2 hours. The young person will need to get themselves to the place where the tests are done.

***(iv) Who else will know the young person is taking part?***

If the young person decides to take part in this project, we will tell their general practitioner or GP.

***(v) What else do I need to know?***

You will be asked to sign a consent form before the young person takes part in the project.

We will also seek your permission to contact Services Australia to find out about the young person's use of medical services and medicines over a 12-month period since taking part in the study.

If you are parent or carer of a young person who is aged between 14-17 years old and do not have a legal guardianship order in place, we will ask you to provide additional documentation to support your permission to contact Services Australia.

(1) a letter from your GP or other suitable health professional stating your young person lacks capacity to make their own medical decisions;
(2) identification documents for both yourself and your young person;
(3) a statutory declaration signed by a Justice of the Peace or equivalent stating you are the best person to have access/control of your young person's records and confirming your relationship to the young person.

Where a child under 14 years of age is on two Medicare cards, both card numbers and the signatures of both primary card holders will need to be on the child's consent form. Data relating to a child's Medicare card will only be supplied where the primary card holder of that card has consented.

You will be asked to sign a consent form authorising the study to access the young person's complete Medicare Benefits Schedule and/or Pharmaceutical Benefits Scheme data as outlined in the consent form. The data we will ask for this study will be for the 12-month period since they took part in the study.

Medicare Benefits Schedule collects information on the young person's doctor visits and the associated costs, while the Pharmaceutical Benefits Scheme collects information on the prescription medications they had filled at pharmacies. The consent form is sent securely to Services Australia who holds Medicare Benefits Schedule and Pharmaceutical Benefits Scheme data confidentially.

The young person's Medicare Benefits Schedule and Pharmaceutical Benefits Scheme data will only be used for the purpose of this research project, these data cannot be used in future research outside of this approved project. However, future research projects that are extensions of or closely related to this project may use other information collected for this project. This information will only be disclosed with your permission, except as required by law. Further, your consent is only specific to participation in this and closely related research projects and does not involve the establishment of a databank.

The young person can continue to do their other usual activities while taking part in the project. The young person will need to tell us what other activities they do. We will let them know if there's an activity they can't do.

## 5 What does it cost?

The young person does not have to pay to take part in this project.

We will:

- Cover the cost of the gym membership for 6 months
- Pay the exercise professional who will help the young person do the exercise program
- Pay $100 in vouchers for attending the testing session
- If the young person lives interstate, we will cover the cost of flights, accommodation and getting to and from the airport up to $1000.

Money will usually be paid to the parent or guardian on behalf of the young person unless you tell us otherwise.

## 6 Other relevant information about the research project

Sixty young people with Prader-Willi syndrome from Australia will be taking part in this project. There are three testing centres in Melbourne, Sydney and Brisbane. People with Prader-Willi syndrome who live outside of these places can take part if they are willing to travel to Melbourne, Sydney or Brisbane to do their tests. We will provide money to people who need to travel to attend their testing sessions.

This project is being done by researchers and health professionals from the following places: La Trobe University, Melbourne; University of Melbourne; University of Sydney; Deakin University, Melbourne; University of Queensland; Royal Children's Hospital, Melbourne; Austin Hospital, Melbourne; Royal Prince Alfred Hospital, Sydney; Queensland Children's Hospital, Brisbane; Princess Alexandra Hospital, Brisbane.

## 7 What are the possible benefits of taking part?

We cannot promise that the young person will receive any benefits from taking part in this project. The young person might find doing exercise improves their fitness. The young person might find their muscles get stronger. The young person might find doing everyday activities might be easier. The young person might enjoy exercising at the gym. The young person might like that they are helping other people with Prader-Willi syndrome by taking part.

## 8 What are the possible risks and disadvantages of taking part?

Exercise can sometimes cause side effects. The young person may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If the young person has any of these side effects, or are worried about them, talk with the researcher. The researcher will also be looking out for side effects.

The risks to the young person are most likely to happen when they start exercising. The most common side effect after starting to exercise is that the young person's muscles get sore. This can happen 1 or 2 days after starting exercise. Sore muscles usually get better quickly and having muscle soreness does not usually stop the young person from exercising again. The researchers will try and minimise the risk of the young person getting muscle soreness by having an exercise professional supervise the exercise program. The exercise professional will help the young person to exercise in the correct way and to use the gym equipment that suits them best. The researcher will tell the young person the best way of easing muscle soreness.

Other side effects that may occur when the young person starts to exercise in the gym may be anxiety about meeting a new person or being in a new place. The exercise professional who will be helping the young person with the exercise program will give them as much support as they need to feel comfortable. The exercise professional will do some training before they start working with the young person to learn about Prader-Willi syndrome. The young person will be encouraged to tell the exercise professional straight away if they feel unwell or uncomfortable when exercising. You or a carer are welcome to attend the exercise sessions with the young person if this will help them.

Many people with Prader-Willi syndrome can have a temper outburst (sometimes called a meltdown) which can happen in any place. It is possible the young person might have a temper outburst when they are doing their exercise program. The exercise professional working with the young person will do their best to communicate clearly with them to help prepare them for what to expect during the exercise program and to signal any changes to the program. They will treat the young person fairly, will avoid rushing them and will do their best to understand what the young person is saying. They will also make sure the young person is safe if they do have a temper outburst and will give them space to calm down.

While the young person is exercising, they will have to work hard and they will likely sweat. The young person will be given time between exercises, if they need to rest.

There may be side effects the researchers do not expect or do not know about and that may be serious. The young person should tell the researchers immediately about any new or unusual symptoms they get. Many side effects go away shortly after exercising. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, the researcher may need to stop the young person from exercising.

This research project involves exposure to a very small amount of radiation. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this research project is about 0.03mSv. At this dose level, no harmful effects of radiation have been demonstrated, as any effect is too small to measure. This risk is believed to be minimal.

Has the young person been involved in any other research studies that involve radiation? If so, please tell us. Please keep information contained within this participant Information and consent form about the young person's exposure to radiation in this study, including the radiation dose for 5 years. You will need to provide this information to researchers of any future research projects involving exposure to radiation.

## 9 Can the young person have other treatments during this research project?

While the young person is taking part in this research project, they can continue to take all their medications or receive their usual medical treatment for their condition or for other reasons. It is important to tell the researchers about any treatments or medications the young person may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell the researcher about any changes to these while the young person is taking part in the research project.

If possible, the young person will be asked not to change their medications while they are in the study. This includes starting on growth hormone therapy. If the young person needs to change their medications during the study, we will ask you to let us know what changes were made so that we can note this.

## 10 What if I withdraw the young person from this research project?

If you withdraw the young person from the study, the researchers will stop paying for the gym membership that the young person received so that they could exercise at the gym as part of the study.

## 11 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:

- Unacceptable side effects
- The treatment being shown not to be effective
- The treatment being shown to work and not need further testing

### 12 What happens when the research project ends?

Within approximately 6 months of the study finishing, the researchers will send a written summary report about the study to the people who took part. If the young person wants a copy of their individual results they will be given these upon written request to the researchers.

## Part 2 How is the research project being conducted?

### 13 What will happen to information about the young person?

In this study we will collect and use personal and health information about the young person for research purposes. We can disclose this information only with your permission, except as required by law.

Information about the young person may be obtained for the purpose of this project from their health records at the hospital where they usually visit their doctor (e.g. Royal Children's Hospital, Melbourne; Austin Hospital, Melbourne; Royal Prince Alfred Hospital, Sydney; Queensland Children's Hospital, Brisbane; Princess Alexandra Hospital, Brisbane). By signing the consent form, you agree to the researchers accessing the young person's health records if it is relevant to their participation in this research project. Information about the young person's participation in this research project may be recorded in your health records.

The young person's information will be used for this research project. We may use the young person's data in future research projects that are closely related to this project.

The following people may access the young person's personal and health information as part of this research project. The:

- research team involved with this project
- Royal Children's Hospital Human Research Ethics Committee who approved the project

The researchers (their names are listed at the start of this document) will have access to the young person's data. In instances where other researchers will need to access the young person's data for future research projects, the University Human Ethics Committee will be advised and requested to grant permission to do so, except as required by law.

We will store the young person's information securely at La Trobe University. We will store the electronic information on secure databases at La Trobe University. We will store the physical information in a locked filing cabinet in the office of Prof Nora Shields at La Trobe University during the project and in a locked archive at La Trobe University after the results of the project have been published.

The young person's information will be identifiable by the researchers. This means the young person's name and other personal details will stay on the information while it is used by the research team. The young person will be given a code number, which will be used when entering data on the computer. Although the researchers will know who the young person is during the project, their name will not be included as part of the results of the project. The young person's identity will remain confidential.

De-identified data from the project will be deposited in the La Trobe University library repository. No one apart from the researchers will have access to re-identifiable data.

We plan to publish the results of this research project in journals and to present them in a variety of places such as at conferences and in workshops. The presentations could take place

in Australia or overseas. The young person's information will be grouped together with the other participants in the project. We will present the findings from the project in such a way that the young person cannot be identified unless you say it is ok for us to do so. If you agree to let us use photographs of you in public presentations, then you could be identified in those pictures.

You have the right to access and to correct the information we collect and store about the young person. This is in accordance with relevant Australian and/or Victorian privacy and other relevant laws. Please contact us if you would like to access this information.

In accordance with regulatory guidelines, the Medicare Benefits Schedule and Pharmaceutical Benefits Scheme data and all other data collected for this project will be kept for 15 years, and then it will be securely destroyed. Paper based data will be put in confidential waste bins available at La Trobe University. Electronic data will be deleted.

## 14 Complaints and Compensation

If the young person suffers any injuries or complications as a result of this research project, you should contact the research team as soon as possible and you will be assisted with arranging appropriate treatment. If the young person is eligible for Medicare, they can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

If you have any questions or complaints about this project you can telephone Prof Nora Shields at La Trobe University, on 03 9479 5852. If you have any complaints or questions that the researchers has been unable to answer, you may contact Alexandra Robertson at the Royal Children's Hospital Human Research Ethics on 03 9345 6924.

## 15 Who is organising and funding the research?

This research project is being conducted by Prof Nora Shields from La Trobe University, Melbourne. The project is being funded by the Medical Research Future Fund of Australia ($869,140).

No member of the research team will receive a personal financial benefit from the young person's involvement in this research project (other than their ordinary wages).

## 16 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of Royal Children's Hospital, Melbourne.

This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). This statement has been developed to protect the interests of people who agree to participate in human research studies.

## 17 Further information and who to contact

If you want any further information concerning this project or if the participant has any medical problems which may be related to their involvement in the project (for example, any side effects), you can contact the principal researcher, Nora Shields, Professor of Physiotherapy at La Trobe University on 03 9479 5852 or n.shields@latrobe.edu.au

For matters relating to research at the site at which the young person is participating, the details of the local site complaints person are:

**Complaints contact person**

| | |
|---|---|
| Name | Dr Zoe McCallum |

| | |
|---|---|
| Position | Consultant Paediatrician, Department of Neurodevelopment and Disability, Royal Children's Hospital |
| Telephone | 03 9345 5522 |
| Email | zoe.mccallum@rch.org.au |

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

**Reviewing HREC approving this research and HREC Executive Officer details**

| | |
|---|---|
| Reviewing HREC name | Royal Children's Hospital Human Research Ethics Committee |
| HREC Executive Officer | Alexandra Robertson |
| Telephone | 03 9345 6 |
| Email | alexandra.robertson@rch.org.au |

If you have a privacy complaint in relation to the use of your Medicare Benefits Schedule (MBS) and/or Pharmaceutical Benefits Scheme (PBS) data you should contact the Office of the Australia Information Commissioner. You will be able to lodge a complaint with them.

Website: www.oaic.gov.au
Telephone: 1300 363 992
Email: enquiries@oaic.gov.au
Mail: GPO Box 5218, Sydney NSW 2001

# Consent Form – Parent/Guardian

| | |
|---|---|
| **Title:** | Improving muscle strength in young people with Prader-Willi syndrome: a phase II randomised trial |
| **Short Title** | Exercise for people with Prader-Willi syndrome (PRESTO trial) |
| **Project Sponsor** | La Trobe University |
| **Principal Investigator** | Prof Nora Shields |
| **Associate Investigator(s)** | Prof Kim Bennell<br>Prof Nicholas Taylor<br>Dr Lauren Rice<br>A/Prof Tania Markovic<br>Prof Chris Bigby<br>A/Prof Jenny Watts<br>A/Prof Luke Prendergast |



## Declaration by Parent/Guardian

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for the young person's doctors, other health professionals, hospitals or laboratories outside this hospital to release information to La Trobe University concerning the young person's condition and treatment including details about their medical visits and prescriptions for the purposes of this project. I understand that such information will remain confidential.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to the young person participating in this research project as described and understand that I am free to withdraw them at any time during the research project without affecting their future health care.

I understand that I will be given a signed copy of this document to keep.

Name of the young person (please print) _____

Signature of the young person _____ Date _____

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date _____

## Declaration by Researcher

I have given a verbal explanation of the research project, its procedures and risks and I believe that the parent/guardian has understood that explanation.

Name of Researcher (please print) _____

Signature _____ Date _____

# Form for Withdrawal of Participation – Parent/Guardian

| | |
|---|---|
| **Title:** | Improving muscle strength in young people with Prader-Willi syndrome: a phase II randomised trial |
| **Short Title** | Exercise for people with Prader-Willi syndrome (PRESTO trial) |
| **Project Sponsor** | La Trobe University |
| **Principal Investigator** | Prof Nora Shields |
| **Associate Investigator(s)** | Prof Kim Bennell<br>Prof Nicholas Taylor<br>Dr Lauren Rice<br>A/Prof Tania Markovic<br>Prof Chris Bigby<br>A/Prof Jenny Watts<br>A/Prof Luke Prendergast |

**Declaration by Parent/Guardian**

I wish to withdraw the young person from participation in the above research project effective from the date below.

Please tick one of the following boxes:

1. ☐ I wish to withdraw the young person from participation and have all their information destroyed from the whole study where possible, including all my Medicare Benefits Schedule (MBS) and/or Pharmaceutical Benefits Scheme (PBS) claims and have no further participation.

2. ☐ I wish to withdraw the young person from participation and have all their Medicare Benefits Schedule (MBS) and/or Pharmaceutical Benefits Scheme (PBS) claims a destroyed from the study where possible, but I am happy for all other information about the young person to be used in the study.

3. ☐ I wish to withdraw the young person from participation but allow all the young person's information including all their Medicare Benefits Schedule (MBS) and/or Pharmaceutical Benefits Scheme (PBS) claims collected up to the withdrawal date to continue to be used in the study.

I understand that:

4. no further information about the young person will be collected for the study from the withdrawal date;

5. the young person's information that has already been collected, and analysed and/or included in a publication, may not be able to be withdrawn or destroyed; and

6. the young person's withdrawal from the study will not affect their routine treatment, their relationship with those treating them or their relationship with La Trobe University.

If you wish to tell us the broad reason why the young person is no longer taking part in the study, please tick the relevant box below:

☐ No longer interested

☐ Circumstances have changed and no longer in a position to take part

☐ Cannot commit the time to take part

☐ There is a medical reason for withdrawing

☐ Other (please specify)……

Name of the young person (please print) _____

Signature of the young person _____ Date _____

Name of Parent/Guardian (please print) _____

Signature of Parent/Guardian _____ Date _____

In the event that the parent/guardian's decision to withdraw is communicated verbally, the researcher will provide a description of the circumstances below.

**Declaration by Researcher†**

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the parent/guardian has understood that explanation.

Name of Researcher† (please print) _____

Signature _____ Date _____

Note: All parties signing the consent section must date their own signature.

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

| Section/item | ItemNo | Description | Manuscript location |
|---|---|---|---|
| **Administrative information** | | | |
| Title | 1 | Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym | p. 1 |
| Trial registration | 2a | Trial identifier and registry name. If not yet registered, name of intended registry | p.3 |
| | 2b | All items from the World Health Organization Trial Registration Data Set | p.1, 3-14; Figure 1, Table 1 and 2 |
| Protocol version | 3 | Date and version identifier | Appendix 1 |
| Funding | 4 | Sources and types of financial, material, and other support | p.15 |
| Roles and responsibilities | 5a | Names, affiliations, and roles of protocol contributors | p.1; 15-16 |
| | 5b | Name and contact information for the trial sponsor | n/a |
| | 5c | Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities | p.15 |
| | 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) | p.13 |
| **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 | p.4-5 |
| | 6b | Explanation for choice of comparators | n/a |
| Objectives | 7 | Specific objectives or hypotheses | p.5 |

| | | | |
|---|---|---|---|
| Trial design | 8 | Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory) | p.5 |
| **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 | p.5-6 |
| Eligibility criteria | 10 | Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists) | p.5 |
| Interventions | 11a | Interventions for each group with sufficient detail to allow replication, including how and when they will be administered | p.6-8 |
| | 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) | p.6 |
| | 11c | Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests) | p.6 |
| | 11d | Relevant concomitant care and interventions that are permitted or prohibited during the trial | p.6 |
| 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 | p.8-9 Table 2 |
| Participant timeline | 13 | Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure) | Figure 1 |
| 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 | p.12 |
| Recruitment | 15 | Strategies for achieving adequate participant enrolment to reach target sample size | p.6 |

**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 | p.5 |
| 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 | p.5 |
| Implementation | 16c | Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions | p.5 |
| Blinding (masking) | 17a | Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how | p.6 |
| | 17b | If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial | n/a |

**Methods: Data collection, management, and analysis**

| | | | |
|---|---|---|---|
| Data collection methods | 18a | Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol | p.8-9, Table 2 |
| | 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 | p.12 |
| Data management | 19 | Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol | p. 12-14 |
| Statistical methods | 20a | Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol | p.12-13 |

| | | | |
|---|---|---|---|
| | 20b | Methods for any additional analyses (eg, subgroup and adjusted analyses) | p.12-13 |
| | 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) | p.12 |
| **Methods: Monitoring** | | | |
| Data monitoring | 21a | Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed | p.13 |
| | 21b | Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial | n/a |
| Harms | 22 | Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct | P 9, Table 2 |
| 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 | p.13-14 |
| Protocol amendments | 25 | Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators) | p. 13 |
| Consent or assent | 26a | Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32) | p.13-14 |
| | 26b | Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable | n/a |
| Confidentiality | 27 | How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial | p.14 |

| | | | |
|---|---|---|---|
| Declaration of interests | 28 | Financial and other competing interests for principal investigators for the overall trial and each study site | p.15 |
| Access to data | 29 | Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators | p.15 |
| Ancillary and post-trial care | 30 | Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation | n/a |
| Dissemination policy | 31a | Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions | p.14 |
| | 31b | Authorship eligibility guidelines and any intended use of professional writers | n/a |
| | 31c | Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code | p.15 |
| **Appendices** | | | |
| Informed consent materials | 32 | Model consent form and other related documentation given to participants and authorised surrogates | Not included for submission but can be provided upon request |
| Biological specimens | 33 | Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable | n/a |

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