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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 that 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.To establish whether 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 two times 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 number ACTRN12620000416998; Australian and New Zealand Clinical Trial Registry.

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 healthcare costs

are high, estimated in 2016 to be €60 k per individual per annum.[9–11]

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 programme 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] demonstrates 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 programme 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 with a waitlist control group. A qualitative study conducted alongside the trial found that 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 whether 6-month community-based progressive resistance training is effective in improving the arm and leg muscle strength of people with PWS. Our secondary aims are to:

1. Determine if progressive resistance training leads to changes in muscle mass, functional strength physical activity, community participation, health-related quality of life and behaviour;
2. Determine if progressive resistance training is cost-effective in people with PWS.
3. 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 1 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) (figure 1). Randomisation will be in a 1:1 ratio with stratification by trial location (Victoria, New South Wales or Queensland) 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 was 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).

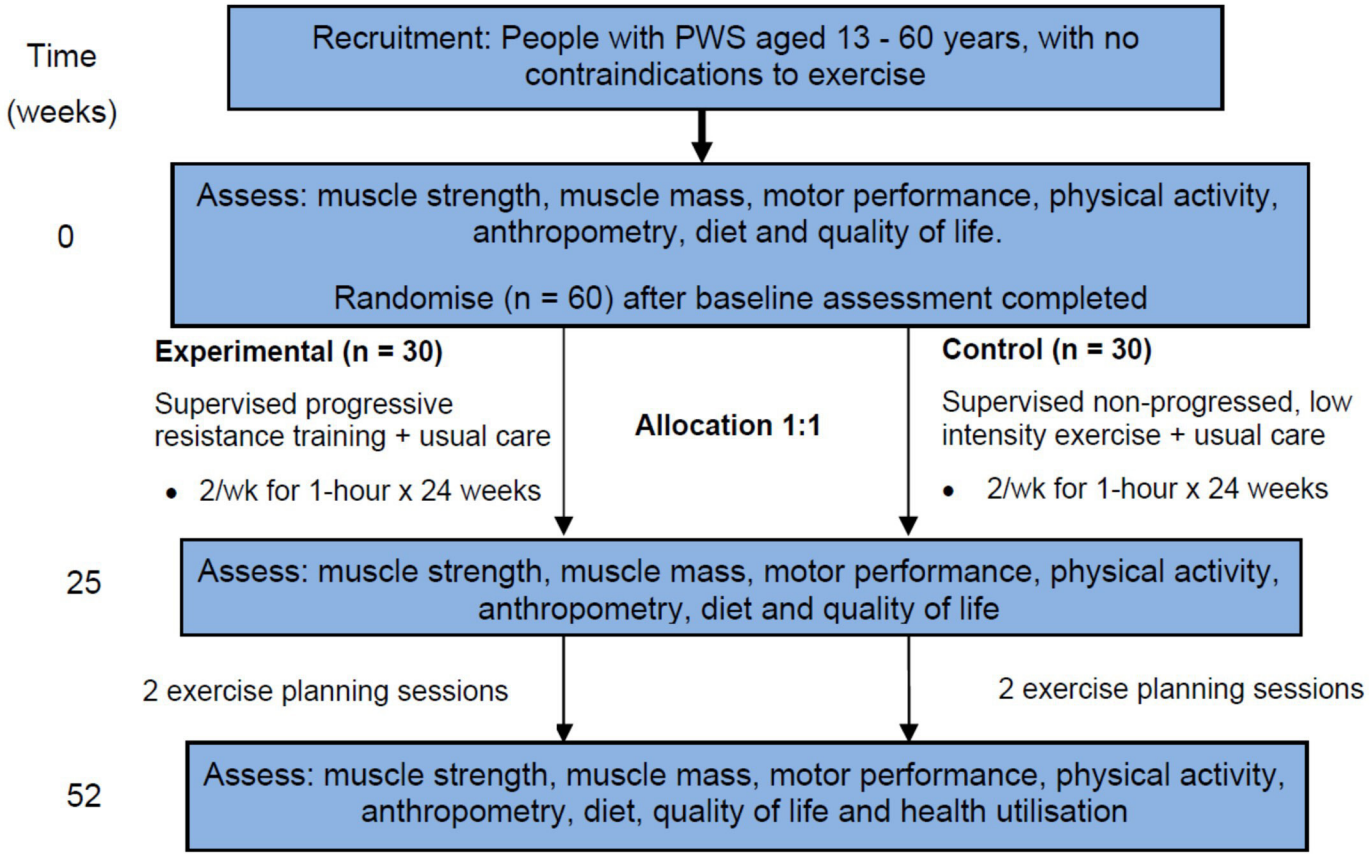

Figure 1 Trial design. PWS, Prader-Willi Syndrome.

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.
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.
2. Have a concurrent physical or mental health condition (eg, severe arthritis, severe psychosis, physically aggressive behaviour) affecting their ability to participate in community-based exercise.

Recruitment

Participants will be recruited through four sources:

1. Population registries or clinical databases (eg, 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.
2. Specialist PWS clinics in Melbourne, Sydney and Brisbane. Potential participants will be informed of the trial by their treating doctor or therapist.
3. PWS advocacy groups based in Australia will send a copy of the flyer advertising the trial to their members.
4. 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.[24] If any concerns related to suitability to take part are identified, they will be asked to obtain medical clearance prior to enrolment (eg, unexplained symptoms such as chest pain or shortness of breath at rest).

Intervention

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

Experimental group

Participants allocated to the experimental group will complete progressive resistance training two times a week for 24 weeks at a community gymnasium (table 1). The programme, designed according to American College of Sports Medicine guidelines,[17] will comprise six exercises: three for the upper limbs (eg, lat pull down) and three for the lower limbs (eg, 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

Table 1 Description of experimental and control group interventions according to the template for intervention description and replication (TIDieR)[57]

	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 (eg, 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 1RM), progressive overload (increase resistance as participant gets stronger) and allow recovery (1–2 min between exercise sets and at least 1 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 programme
Who provided	An exercise professional (eg, 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 min duration over 24 weeks (total 48 hours)	
Tailoring	Resistance will be tailored to the individual (60–80% of their 1RM of each exercise).	If necessary, to maintain a participant's interest, skills-based exercise may be incorporated into the programme
Fidelity checking measures	Adherence to the protocol parameters of attendance, exercise type, intensity and volume, rest periods, and programme frequency, duration and progression documented at each session in an online logbook (using REDCap software)	

1RM, 1 repetition maximum .

12 repetitions of each exercise until fatigue (intensity of 60%–80% of 1 repetition maximum, 1RM). A 2 min 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 1 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 programme 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.

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 programme. 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 4 weeks and the second session within 12 weeks of programme 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 and Brisbane).

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	DXA licenced clinician	✓	✓	✓
Functional strength	Sit-to-stand	Time taken to stand up and sit down five 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 two attempts	Clinician observation	✓	✓	✓
	6 min walk test	Distance walked in 6 min over a 25 m course. Continuous encouragement allowed.	Clinician observation	✓	✓	✓
Physical activity	Daily total physical activity Daily steps Daily time sedentary	Daily total physical activity Daily steps 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 activities	Questionnaire, self-report or proxy-report	✓	✓	✓
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			✓

Continued

Table 2 Continued

Outcome	Measure	Description	Administration	Week 0	Week 25	Week 52
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 programme 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		✓	

CHU-9D, Child Health Utility; PEM-CY, Participation and Environment Measure-Children and Youth; QI-Disability, Quality of Life Inventory-Disability ; 1RM, 1 repetition maximum .

Primary outcome measure

Muscle strength will be assessed using 1 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 (Intra-class correlation coefficient (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 min 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 1 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] 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 15–17 years.[31] The Adolescent Sedentary Activity questionnaire has good to excellent reliability (ICC=0.57 to 0.86) and good face validity in Australian adolescents aged 11–15 years.[32] 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 5–17 years.[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] The CHU-9D has evidence of criterion validity (Spearman's ρ=0.61) in Australian adolescents aged 11–17 years[37] and good retest reliability in children with inflammatory bowel disease aged 6–18 years (ICCs 0.71 to 0.89).[38] The QI-Disability questionnaire, developed for Australian children aged 5–18 years with intellectual disability across four diagnostic groups (Rett syndrome, Down syndrome, cerebral palsy and 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).[39]

Behaviour will be assessed using the parent-report Developmental Behaviour Checklist,[40] which measures overall behavioural and emotional disturbance and five 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 1 year.

Other outcomes

Demographic data on age, sex, medications (including growth hormone), comorbidities, 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 (V.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.[41 42] Participants will be asked to talk about aspects of the programme 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.

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[43] including whether improvements in muscle strength) are mediated by changes in muscle mass and other factors associated with variation in outcomes.[44] The Consolidated Standards of Reporting Trials 2010[45] and the consensus on exercise reporting template[46] guidelines will guide reporting.

Analysis of qualitative outcomes

The theoretical framework underpinning the qualitative data analysis is interpretive description.[47] 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 programmes for people with PWS rather than creating new theory. The Consolidated criteria for Reporting Qualitative research checklist[48] 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.[49] 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 is 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. Programme 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) used following completion of the intervention for both groups up to week 52. The incremental cost-effectiveness ratio around the primary outcome will be calculated as the difference in total programme and health service costs between the groups over 1 year. A cost utility ratio will be calculated based on the secondary outcome measure as the change in total programme and health service cost per change in quality adjusted life years saved in the experimental and control groups over 1 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 programme length; on the effect side health-related quality of life and muscle strength. The Consolidated Health Economic Evaluation Reporting Standards will guide reporting.[50]

Patient and public involvement

This proposal was codeveloped 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 serious 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 and 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.[51] In this case, the adult with PWS is also invited to provide their own written consent (online supplemental appendix 2). For adolescents with PWS (13–17 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 judgement. 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 programmes for people with cognitive disability and behavioural challenges, a knowledge translation plan guided by the Practical Robust Implementation and Sustainability Model[52] 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 programmes 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 (eg, residential care facility staff) on how community exercise programmes 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 (eg, newsletters, blogs, social media, public talks) and health professionals (eg, publications, presentations). The contribution of the participants with PWS will be directly acknowledged. Consistent with Australian National Health and Medical Research Council policies, deidentified data from the trial will be made available through, 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.[53] 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.[3] 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 programme 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 RCTs to address the disconnect between research and practice.[54] There is limited literature available to support the design and delivery of exercise programmes 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.[55] 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.[56] A further limitation is that although participants and assessors will be blinded to group allocation, it is not possible to blind exercise professionals.

This RCT 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.

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.

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Contributors 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. KLB, LJR, TM, CB, NFT 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. JJW 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, ZMC, 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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