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Rehabilitation for ataxia study: protocol for a randomised controlled trial of an outpatient and supported home-based physiotherapy programme for people with hereditary cerebellar ataxia

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ABSTRACT

Introduction Emerging evidence indicates that rehabilitation can improve ataxia, mobility and independence in everyday activities in individuals with hereditary cerebellar ataxia. However, with the rarity of the genetic ataxias and known recruitment challenges in rehabilitation trials, most studies have been underpowered, non-randomised or non-controlled. This study will be the first, appropriately powered randomised controlled trial to examine the efficacy of an outpatient and home-based rehabilitation programme on improving motor function for individuals with hereditary cerebellar ataxia.

Methods and analysis This randomised, single-blind, parallel group trial will compare a 30-week rehabilitation programme to standard care in individuals with hereditary cerebellar ataxia. Eighty individuals with a hereditary cerebellar ataxia, aged 15 years and above, will be recruited. The rehabilitation programme will include 6 weeks of outpatient land and aquatic physiotherapy followed immediately by a 24- week home exercise programme supported with fortnightly physiotherapy sessions. Participants in the standard care group will be asked to continue their usual physical activity. The primary outcome will be the motor domain of the Functional Independence Measure. Secondary outcomes will measure the motor impairment related to ataxia, balance, quality of life and cost-effectiveness. Outcomes will be administered at baseline, 7 weeks, 18 weeks and 30 weeks by a physiotherapist blinded to group allocation. A repeated measures mixed-effects linear regression model will be used to analyse the effect of the treatment group for each of the dependent continuous variables. The primary efficacy analysis will follow the intention-to-treat principle.

Ethics and dissemination The study has been approved by the Monash Health Human Research Ethics Committee (HREC/18/MonH/418) and the Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (2019/3503). Results will be published in peer-reviewed journals, presented at national and/or international conferences and disseminated to Australian ataxia support groups.

Trial registration number ACTRN12618000908235.

Strengths and limitations of this study

- This single-blinded randomised controlled trial will compare a 30-week combined outpatient and home-based rehabilitation programme to 30 weeks of standard care in Australia for people with a hereditary cerebellar ataxia.
- Ambulant and non-ambulant individuals will be recruited, with mobility ranging from difficulty tandem walking to requiring minimal assistance with transfers.
- The rehabilitation programme will include land and aquatic physiotherapy, incorporating six domains of rehabilitation, and will be individualised to each participant.
- A cost-effectiveness analysis will be undertaken comparing the rehabilitation programme to standard care.
- The 'standard care' received by participants in the control group may comprise of varied exercise intensity (up to a maximum of 3 hours per week) potentially resulting in a reduced effect size for the rehabilitation programme.

INTRODUCTION

Hereditary cerebellar ataxias encompass a group of rare genetic disorders associated with degeneration of the cerebellum and consequent progressive ataxia.[1] The disorders can be characterised by mode of inheritance and gene impacted,[2] with the majority transmitted through an autosomal dominant or autosomal recessive inheritance.[3]

Autosomal dominant cerebellar ataxia is estimated to affect 2.7 in 100 000 and autosomal recessive cerebellar ataxia 3.3 in 100 000 people across the world.[4] The main clinical features of hereditary cerebellar ataxia are typically gait and limb ataxia, impaired balance, oculomotor incoordination and dysarthria.[5 6] Progressive gait ataxia often leads to reduced mobility and functional independence in daily activities, with a significant negative impact on quality of life.[7 8]

While the cerebellum is the unifying site of pathology in the hereditary cerebellar ataxias, the clinical phenotype differs between and within the ataxias. Extracerebellar pathology often coexists alongside cerebellar degeneration.[5] This may include extrapyramidal, pyramidal, brainstem, spinocerebellar tract, dorsal column, basal ganglia, vestibular and peripheral nerve pathology.[9 10] Many hereditary cerebellar ataxias are due to nucleotide repeat expansions while others are due to point mutations and deletions or duplications. Repeat expansion size and other unknown factors cause the variations in age of symptom onset, clinical severity and rate of disease progression within ataxias.[9]

Presently no pharmacological treatment has been conclusively shown to slow or halt disease progression in the hereditary cerebellar ataxias,[11] although research into treatment has advanced considerably over the last two decades.[12] Multidisciplinary allied health involvement and rehabilitation therapies including physiotherapy and prescribed exercise programmes are therefore used to manage the symptoms, prevent secondary complications such as falls and, in some instances, have shown a regain in function of at least 2 years of natural disease progression.[13–16] It is suggested that greater frequency of exercise and challenging balance produce better outcomes for individuals with hereditary cerebellar ataxia.[14 17–19] Inpatient and outpatient rehabilitation programmes typically offer more intensive rehabilitation than community or home-based options. However, due to rising healthcare costs and the progressive nature of the hereditary cerebellar ataxias, low-cost home-based programmes are often prescribed by clinicians[20] and implementation of more intensive outpatient treatment in clinical practice remains limited.[21]

Recent systematic reviews have identified over 20 studies examining rehabilitation, physical therapy or exercise for individuals with ataxia.[15 22 23] Resoundingly these studies demonstrated improvements in ataxia, function, balance and/or mobility after rehabilitation, indicating positive outcomes for individuals with a hereditary cerebellar ataxia. However, most studies are prospective or retrospective cohort studies, quasi-randomised trials and case series. Seven randomised controlled trials examining rehabilitation have been conducted.[14 24–29] The conclusions that can be drawn are limited by underpowered sample sizes,[14 24 25 27] an absence of between-group statistical analyses[24 25] and no long-term follow-up[14 25 27–29] in many of the studies. The rarity of the hereditary cerebellar ataxias in combination with the challenges related to recruitment in rehabilitation trials[30] is the likely factor for the absence of high-quality and appropriately powered randomised controlled trials in this clinical area.

This study aims to provide the first appropriately powered randomised controlled trial examining a combined outpatient rehabilitation and supported home exercise programme as compared with usual care for individuals with hereditary cerebellar ataxia. This rehabilitation intervention is structured to provide 6 weeks of intensive land and aquatic outpatient physiotherapy followed by a 6-month lower resourced, physiotherapist-supported, home-based exercise programme designed to augment and sustain the functional gains made in the first part of the study. It is hoped that this study will provide conclusive evidence of the role of structured rehabilitation programmes in clinical care of patients with ataxia.

Aims and objectives

Primary aim

- To determine the effect of a 30-week individualised rehabilitation programme (6 weeks of intensive outpatient rehabilitation followed by 24 weeks of a supported home exercise programme) on motor function (measured by the motor domain of the Function Independence Measure (m-FIM)) as compared with standard care for individuals with a hereditary cerebellar ataxia.

Secondary aims

- To evaluate the effect of the 30-week rehabilitation programme on a range of other neurological outcomes and patient perceived benefit as compared with standard care.
- To assess the cost-effectiveness of the 30-week rehabilitation programme compared with standard care by reporting an incremental cost per quality-adjusted life year (QALY).

Study design

This is a randomised, single-blind, parallel group trial comparing a 30-week rehabilitation programme (intervention group) to standard care (control group). The rehabilitation programme will include 6 weeks of outpatient rehabilitation followed by a 24-week physiotherapy-supported home exercise programme. Participants will be assessed at four time points by a physiotherapist with 6 years or greater of neurological experience, blinded to group allocation: (1) immediately prior to the rehabilitation programme or standard care commencement (baseline), (2) at 7 weeks, corresponding to immediately after completion of the outpatient programme or after 6 weeks of standard care, (3) 18 weeks, corresponding to half way through the supported home exercise programme or after 18 weeks of standard care and (4) 30 weeks, corresponding to immediately after cessation of the supported home exercise programme or after 30 weeks of standard care. These time points will allow an individual evaluation of the outpatient component of

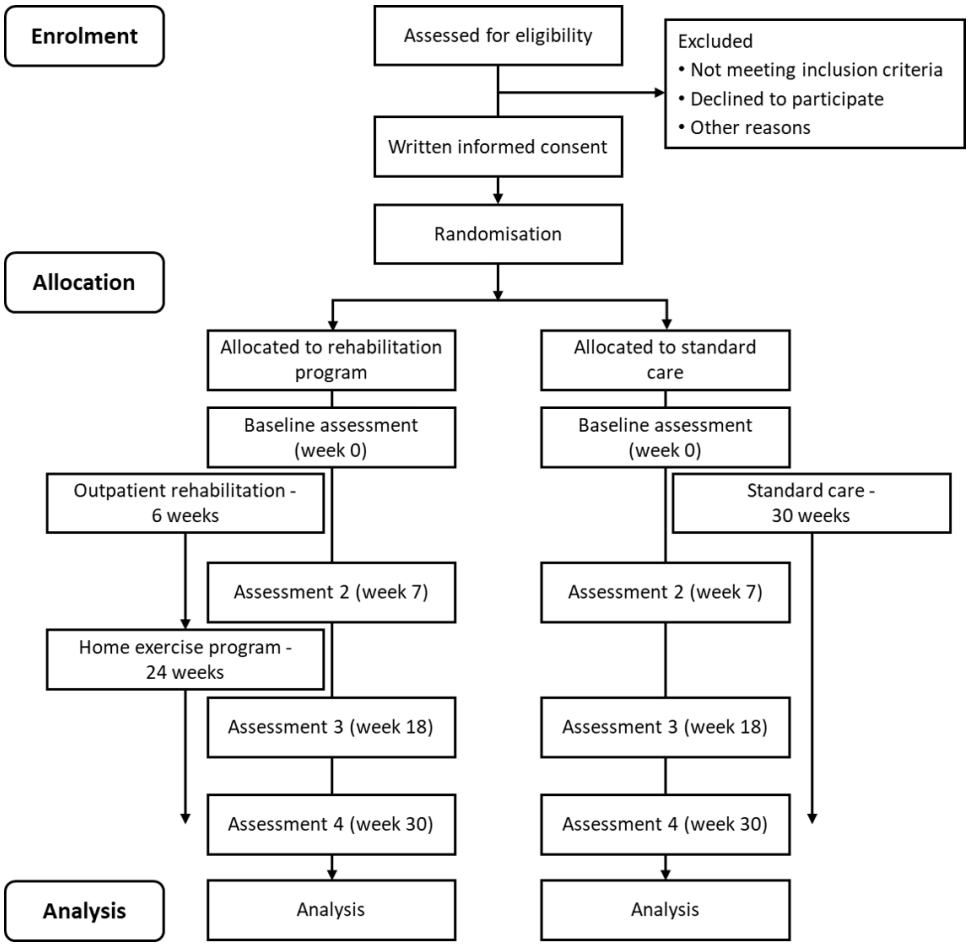

Figure 1 Participant flow through the study.

the rehabilitation as well as an evaluation of the effectiveness of the supported home exercise programme to sustain and/or augment the benefits of the outpatient programme at the 18-week and 30-week time points. Given the nature of the intervention, participants cannot be blinded.

Randomisation and allocation

The randomisation sequence will be created using a password-protected central randomisation tool linked to the Murdoch Children's Research Institute's instance of the Research Electronic Data Capture (REDCap) (http://project-redcap.org/) database[31 32] with a 1:1 allocation using random block sizes of two and four. An independent statistician will create random allocation tables using block randomisation that will be uploaded to the randomisation tool. The allocation and allocation tables will be concealed from the investigators enrolling the participants. Each participant's personal information will be entered into the REDCap database by the enrolling investigator after written consent is provided. The randomisation tool will then disclose the group allocation to the enrolling investigator. See figure 1 for the Consolidated Standards of Reporting Trials flowchart of this trial.

Study setting

The rehabilitation programme will be conducted at five Australian sites: Kingston Centre, Melbourne; Ryde Hospital, Sydney; Sir Charles Gairdner Hospital, Perth; Palmerston Regional Hospital and the Machado-Joseph Disease Foundation Office, Darwin and the Machado-Joseph Disease Foundation Office, Groote Eylandt.

Study population

Participants will be eligible if they have a recessively or dominantly inherited cerebellar ataxia and have a level of motor function ranging from difficulty with tandem walking (minimum disability) to unable to walk and requiring minimal assistance with transfers (maximum disability). Full eligibility criteria are listed in box 1.

Participant screening, recruitment and consent

Six methods will be used to identify and recruit participants.

1. Potential participants will be identified through the established clinical research programme (including the Collaborative Clinical Research Network in Friedreich Ataxia (CCRN) and/or being registered with the Friedreich Ataxia Clinic at Monash Medical Centre (Melbourne), the Alfred Health Cerebellar Ataxia

Box 1 Eligibility criteria

Inclusion criteria

- Individuals with a molecular diagnosis, or at least three generations affected, of a recessively or dominantly inherited cerebellar ataxia.
- Aged over 15 years.
- Mobility ranging from:
  A minimum score of 2 for question 1 'gait' of the Scale for the Assessment and Rating of Ataxia (2=gait clearly abnormal, tandem walking>10 steps not possible). (A score of 2 is the maximum level of mobility allowable).
  A minimum score of 4 for item I 'transfers bed, chair, wheel-chair' of the functional independence measure (4=minimal assistance, the participant completes 75% or more of the task). (A score of 4 is the minimal level of mobility allowable).
- Given clearance by cardiologist or other appropriate medical professional for participation in the rehabilitation programme.

Exclusion criteria

- Musculoskeletal injury limiting ability to weight bear.
- Another medical condition that impacts on mobility.
- Undergone major orthopaedic surgery in the last 6 months.
- Need for immediate intensive intervention for safety reasons.
- Pregnancy.
- Significant cognitive impairment limiting ability to give informed consent and/or participate in the rehabilitation programme.
- Received botulinum toxin injections for spasticity management within the last 3 months (with the exception of regular longstanding paraspinal botulinum injections—defined as at least two doses of botulinum injections in the same muscle/s within 8 months of the screening period).
- Already completing greater than 3 hours per week of lower limb/lower body physical exercise/therapy (ie, pilates, personal trainer, home exercise programme, independent gym programme, exercise physiology) or is participating in a structured goal-based physiotherapy rehabilitation programme. This does not include physical activity that occurs as part of the person's daily life, for example, walking to a shopping centre.
- Currently enrolled in another clinical trial or planned enrolment in another clinical trial during the period of the study.
- Has a medical condition that precludes entry into a hydrotherapy pool.

Clinic (Melbourne) and the Victorian Clinical Genetic Service (Melbourne). The initial screening process will be undertaken by a member of the research team. A letter or email of invitation and information on the study will be sent to these potential participants.

2. Information on the study will be advertised via email and at meetings via Australian ataxia support groups including: Friedreich Ataxia Association of Victoria, Friedreich Ataxia Research Association (FARA) Australia, Friedreich Ataxia Network, Cerebellar Ataxia Australia and Machado-Joseph Disease Foundation.
3. Potential participants will be identified at the following patient clinics: the Friedreich Ataxia, Neurogenetics and Neurology Clinics, Monash Medical Centre, Melbourne; Cerebellar Ataxia Clinic, Caulfield Hospital, Melbourne; Neurogenetics and Neurology Clinics, Royal Melbourne Hospital, Melbourne; Neurology and Neurogenetic Clinics, Royal Children's Hospital, Melbourne; Neurogenetics Clinic, Royal North Shore Hospital, Sydney; Neuromuscular/Neurogenetic Clinic, Concord Repatriation General Hospital, Sydney; Neurogenetic Clinic, Royal Perth Hospital, Perth; and Neurology Clinic, Royal Darwin Hospital, Darwin. Potential participants will be approached and provided with study information during their attendance by the neurologist or geneticist working in those clinics.
4. Information about the study will be provided to private neurologists and physiotherapists working in Melbourne, Sydney, Perth and Darwin. In addition, study information will be provided to the Australasian Neuromuscular Network and advertised through the e-bulletin of the Australian and New Zealand Association of Neurologists.
5. Potential participants will be identified through the Victorian Clinical Genetic Service or the Molecular Medicine Department, Concord Repatriation General Hospital, who conduct testing for hereditary cerebellar ataxias including Friedreich ataxia and spinocerebellar ataxia types 1, 2, 3, 6 and 7. A letter with study information will be sent to the patient's referring doctor to discuss with the potential participant.
6. Individuals will be identified through the Victorian Clinical Genetic Service or the Molecular Medicine Department, Concord Repatriation General Hospital, clinical genetic files. Patients with a hereditary cerebellar ataxia from the past 20 years will be identified and a letter or email will be sent to these potential participants.

In addition, individuals currently not known to any of the above will be recruited through 'snowball recruitment' of affected relatives of recruited individuals. Interested people will be invited to contact the research team to discuss the study further, express their interest in participating and determine eligibility. All participants will be provided with written information on the study. If they agree to participate, they will be invited to attend a consultation with the site principal investigator to obtain their (and/or their parent's/guardian's) written informed consent as per the Declaration of Helsinki. (See online supplemental file 1 for Master Patient Information and Consent Form.) They will then be enrolled in the study.

Intervention

Intervention group

Participants in the intervention group will receive a 30-week individualised rehabilitation programme targeted at improving motor function, mobility and balance. The programme will include 2 hours of outpatient physiotherapy, three times per week, for 6 weeks, followed by a 24-week independent home exercise programme supported with fortnightly physiotherapy sessions.

The outpatient component will be conducted on land (1 hour) and in a hydrotherapy pool (1 hour) and is based on the treatment programme of our pilot study.[14] The

intervention will be provided by a physiotherapist with 6 or more years of neurological clinical experience, on a one-to-one basis. The physiotherapist will be supported by an allied health assistant. To provide the individualised rehabilitation programme, the treating physiotherapist will work with the participant to determine three functional goals (using the Goal Attainment Scale[33]) and will conduct a thorough assessment of the participant's function and impairments. At the cessation of the outpatient component, the physiotherapist will devise a home-based exercise programme for the participant.

The home component will require participants to exercise for 1 hour, 5 days per week. Fortnightly physiotherapy support will be provided via alternating home visits and teleconference sessions. The fortnightly support will entail: running through the exercise programme; progressing or modifying the programme as appropriate; answering participant queries regarding the programme; providing education and support regarding mobility issues that arise; providing encouragement to complete the programme and providing advice on barriers to programme completion. It is anticipated that this support will address the challenges with adhering to a home-based programme. It is based on successful models in Charcot-Marie-Tooth disease[34] and Parkinson disease[35] designed to maximise exercise completion.

The rehabilitation programme will be founded on six domains[14] of rehabilitation: (1) strengthening, (2) postural control, (3) functional mobility, (4) balance training, (5) coordination and control and (6) sensory stimulation, mobilisation and stretching and vestibular rehabilitation. Table 1 summarises the key characteristics and rehabilitation time allocated to each domain. All therapy/exercises provided will be chosen from a working list of treatment and exercise options classified into the six domains (see online supplemental appendix 1). Appropriate selection will be determined by the physiotherapist using professional clinical reasoning. Online supplemental appendix 2 provides further prompts for exercise selection, clinical reasoning and management of the rehabilitation programme.

Exercises will be progressed according to each participant's progression in the performance of each exercise, their fatigue and motivation levels and their goals. During the intervention period, fortnightly clinical reasoning meetings with the physiotherapists from each site will standardise and assist with exercise selection, clinical reasoning and progression. An interpreter (or

Table 1 Key characteristics and time allocation of the rehabilitation domains

		Time spent per session (minutes)	
Domain	**Key characteristics**	**Outpatient component**	**Home component**
Strengthening	Strengthening exercises performed in standing, sitting or lying with a focus on lower limb extensors and trunk muscles. Intensity of training based on a protocol designed for individuals with multiple sclerosis, with participants performing 3–5 sets of 6–12 repetitions at 6–15 repetition maximum.[54] There will be a focus on maintaining correct movement patterns and eccentric control during all exercises. Physiotherapist-facilitated movement will be used if participants have insufficient muscle strength.	35	15
Postural control	Physiotherapist-facilitated and independent performance of selective pelvic, trunk and scapular movements, as well as rotational control in the hydrotherapy pool. Upper limb movement with postural control will be included.	20	10
Functional mobility	Practice and part-practice of functional movements, such as walking and lying to sitting. The hydrotherapy pool will be used for dynamic walking practice, including turning and stopping.	20	10
Balance training	Dynamic and static standing for ambulant participants and dynamic and static sitting balance for non-ambulant participants. Differing surfaces (foam, wobble board, exercise ball or balance disc) used to add balance challenge.[19] This domain will be completed on land and in the hydrotherapy pool.	20	15
Coordination and control	Eccentric movement control in combination with whole-body movements[17] and physiotherapist-facilitated movements of the lower limbs.	15	5
Sensory stimulation, mobilising and stretching	Sensory stimulation provided through active and passive foot and ankle mobilisation.[55] Standing exercises will be completed barefoot to enhance somatosensory feedback. Passive mobilising and stretching provided and incorporated immediately into active and functional training.	10	5

community support worker, as appropriate) will be used to assist with the rehabilitation if required.

All physiotherapy sessions will be documented by the treating physiotherapist. This will include the exercise or therapy chosen, exercise progressions and rationale for progression. A home exercise programme diary will be completed by participants (and/or their caregivers if required) to record their exercise completion at home. The physiotherapist will collect the diary content at each fortnightly physiotherapy session.

Control group

Participants will receive their usual (standard) allied healthcare and be asked to continue their usual activities and exercise for the 30 weeks. In Australia, standard care varies, ranging from annual reviews by a multidisciplinary team who recommend and prescribe home exercises,[20] to attending gym, physiotherapy or exercise physiology sessions 3–4 times per week. Standard care will be monitored and deviations (greater than 3 hours per week of lower limb/lower body physical exercise or treatment or participation in a structured goal-based physiotherapy rehabilitation programme) collected through discussion with the participant at their baseline, 7-week, 18-week and 30-week assessments.

If it is identified that a referral to other services (such as occupational therapy for wheel-chair prescription or orthotists/podiatrists for orthotic prescription) is required, the physiotherapist will provide a recommendation to the relevant service to initiate a referral. This will occur as per standard practice for participants in both groups.

Outcomes

The primary outcome measure will be the m-FIM.[36 37] Scores will be attained by an FIM-certified assessor through structured interview with the participant[38] and observation during the assessment. Secondary outcome measures are: Scale for the Assessment and Rating of Ataxia[39]; Berg Balance Scale[40]; Patient Global Impression of Change (PGIC)[41]; Medical Outcomes Study 36 item Short-Form Health Survey V.2 (SF-36 v2)[42]; Function in Sitting Test[43]; postural control in sitting and standing with eyes open and eyes closed measured with the BioKin system[44] and average daily step count and distance travelled measured with the Fitbit Flex 2 (Fitbit, San Francisco, California, USA) over a 7-day period. See table 2 for details of outcome measures.

Demographic details, disease characteristics, the presence of a sensory impairment, current medications and baseline exercise and physical activity will be collected. This will include: (1) age, (2) sex, (3) age of onset of disease symptoms, (4) diagnosis, (5) repeat size(s) for those whose ataxia is a nucleotide repeat expansion disorder, (6) ambulation status and use of mobility aids including wheel-chair, (7) below knee pin-prick, (8) vibration sense of the distal phalanx of the hallux, (9) joint position test of distal interphalangeal joint of hallux, (10) current medications taken, (11) the Phone-FITT,[45] a questionnaire measuring physical activity and (12) summary of current weekly exercise and sport undertaken. The presence of a sensory impairment is measured due to its frequent co-occurrence in people with hereditary cerebellar ataxias[46] and its potential influence on the effects (magnitude and ability to sustain improvement) of rehabilitation.[17] Impaired sensation will be defined as any incorrect answers (out of six) during the pin-prick or joint position test, left or right sides and vibration sense of less than 15 s.[47]

An interpreter (or community support worker, as appropriate) will be used to assist with patient-reported measures if required. Participants will be asked to avoid discussing their group allocation with the blinded assessor and a survey will be undertaken by the assessor after each assessment to monitor their awareness of the participant's group allocation. To ensure inter-rater reliability of the outcome measures, 20 participants from the Melbourne site will have their baseline assessments video-recorded. All physiotherapist assessors will score the assessment and discrepancies in scores will be discussed until inter-rater reliability is acceptable (Intraclass Correlation Coefficient>0.80).

Safety outcomes

Three safety outcomes will be evaluated fortnightly: fatigue will be measured with the Fatigue Severity Scale[48]; falls history and quantity will be measured according to the Ashburn and colleagues'[49] interview script and the European consensus definition[50] and pain lasting greater than 72 continuous hours and/or impacting on function will be documented. Participants may be withdrawn from treatment if rehabilitation is contraindicated due to a new diagnosis or change in health status. The treating physiotherapist will use clinical reasoning to determine this, as per usual clinical practice.

An adverse event is defined as any untoward medical occurrence in a participant regardless of its causal relationship to the study treatment except if it is present at the baseline assessment and does not deteriorate during the study enrolment. Adverse events will be classified as serious or non-serious. See box 2 for serious adverse event definition.

Sample size calculation

The sample size calculation is based on m-FIM data from our previous study.[14] Forty participants per group will be required to detect an increase of the m-FIM by 2.5 points or more (SD=3.3) in the intervention versus 0.0 (SD=3.9) in the control group, assuming a 15% drop out at 30 weeks, a two-tailed type I error of 5% and 80% powers.

Clinical relevance

With an anchor-based method to compare m-FIM scores to the PGIC, with a cut-off score of five deemed a meaningful improvement, the available data from our previous

Table 2 Outcome measures and psychometrics properties

Outcome	Measure	Description	Psychometric properties
Motor function	m-FIM[37]	► The m-FIM evaluates a person's ability to perform motor activities of daily living.[56] Items include performance in self-care, sphincter control and mobility.[57] ► 13 items, each assessed against a 7-point ordinal scale. ► Maximum score of 91 (complete independence) and a minimum of 13 (complete dependence).	► High validity and inter-rater reliability[36 58]. ► More responsive to change after rehabilitation than the total FIM score for individuals with FRDA.[14] ► Exhibited strong correlations with level of disability in neurological populations and can predict amount of help required.[36 59–61]
Ataxia symptoms	SARA[39]	► The SARA is a semiquantitative clinical assessment of ataxia, measuring ataxia of upper limb, lower limb, gait, balance and speech. ► Eight items; score range 0–40, with a higher score indicating more severe ataxia.[39]	► Excellent inter-rater and test–retest reliability in individuals with ataxia.[39] ► Excellent construct validity in ataxias of multiple aetiologies[62 63].
Balance	BBS[40]	► The BBS evaluates performance in sitting and standing balance activities. ► 14 items; score ranging 0–56 with a higher score indicating better balance.	► Responsive to change after intensive coordinative training in degenerative ataxias.[17] ► Good intra- and inter-rater reliability when assessing balance in people with ataxia secondary to multiple sclerosis.[64]
Participant perceived benefit	PGIC[41]	► The PGIC is 7-point numerical rating scale measuring global benefit from the participant's perspective. ► Maximum score of 7 (a great deal better, and a considerable improvement that has made all the difference) and a minimum of 0 (no change). ► Cut-off for clinically meaningful change will be 5 (moderately better, and a slight but noticeable change).	► High face validity.[65] ► Responsive to change following a 6 week rehabilitation programme in individuals with FRDA.[14] ► Used as an external criterion for determining smallest detectible and clinically meaningful change after rehabilitation and 1 year of natural decline in individuals with multiple sclerosis and spinocerebellar ataxia respectively[66 67].
Quality of life	SF-36 v2[42]	► The SF-36 v2 measures self-perceived health-related quality of life. ► 36 items; yields scores for eight multiitem dimensions and two summary scale scores (physical and mental health).[42]	► Responsive to reduction in quality of life in individuals with ataxia[68 69]. ► The physical component of the SF-36 v2 has been shown to be highly correlated with disease duration and ataxia severity in individuals with FRDA.[68] ► The Sf-36 v1 has shown acceptable internal consistency among subscales in individuals with FRDA.[70]
Daily walking activity	1. Average daily step count. 2. Average daily distance walked.	► Measured with the Fitbit Flex 2, a commercial grade tri-axial accelerometer worn on the wrist. ► Worn for 24 hours per day for seven consecutive days. ► A valid day=Fitbit Flex 2 worn for ≥90% of the day. Wear time will be recorded by participant self-report.	► 3–5 days of accelerometer monitoring in adults is necessary to achieve a between day intra-class correlation of 0.80.[71] ► Moderate validity for measuring physical activity relative to the Actigraph.[72] Good to excellent significant positive correlations and agreement with the Actigraph, although it overestimates number of steps.[73] ► Excellent reliability in an older population.[74]

Continued

Table 2 Continued

Outcome	Measure	Description	Psychometric properties
Sitting balance	FIST[43]	► The FIST is a clinical measure of sitting balance.[43] ► 14 items; score ranging 0–56 with a higher score indicating better sitting balance.[43]	► Excellent concurrent validity with the BBS and moderate to good validity with the m-FIM in adults with neurological deficits and impaired sitting balance.[75] ► Excellent test–retest reliability in individuals with various neurological disorders[76 77]. ► Responsive to change following rehabilitation and a minimal detectible change of 5.5 points.[75]
Postural control	3D movement of the trunk in sitting and standing with eyes open and closed.	► Measured with the BioKin system, a wireless motion capture device.[44] ► Four test conditions include: sitting 30 s, no foot contact on the floor, arms out straight: (1) eyes open and (2) eyes closed; standing 30 s, feet together: (3) eyes open and (4) eyes closed.	► An exploratory outcome used in this trial, not previously validated in this population.

BBS, Berg Balance Scale; 3D, three-dimensional; FIST, Function in Sitting Test; FRDA, Friedreich ataxia; m-FIM, motor domain of the functional independence measure; PGIC, Patient Global Impression of Change; SARA, Scale for the Assessment and Rating of Ataxia; SF-36 v2, Medical Outcomes Study 36 item Short-Form Health Survey V.2.

study[14] identified a Minimal Clinically Important Difference (MCID) of four points. A four-point change in the m-FIM relates to an improvement in independence on four activities of daily living; is deemed clinically relevant in chronic multiple sclerosis[51] and is at least a reversal of the equivalent of 2 years of annual disease progression in individuals with Friedreich ataxia (unpublished data). As this study is powered to detect a change of 2.5-points or more in the intervention group, it is also powered to detect the MCID of a four-point improvement in the m-FIM.

Data analysis plan

A repeated measures mixed-effects linear regression model will be used, including the fixed effects group (intervention, control) and time (baseline, week 7, week 18, week 30) and stratification variable (Melbourne, Sydney, Perth, Darwin, Groote Eylandt) and a random effect for individual study participants to analyse the effect of treatment group for each of the dependent continuous variables. The primary efficacy analysis will follow the intention-to-treat principle. Reasons for withdrawal will be recorded.

The intervention effect on the primary outcome, m-FIM, will be estimated as the mean difference in the m-FIM along with 95% CI levels between the intervention and control groups. Where variables are skewed, transformations will be performed to generate more normally distributed variables. If no transformation is possible, the data will be analysed using non-parametric methods, such as the Mann-Whitney U-test to compare outcomes in the two treatment arms. Subgroup analyses will be conducted in participants with and without sensory impairment as established at baseline testing. Statistical analysis will be performed using Stata (V.15 or later; Stata, College Station, Texas, USA).

Box 2 Criteria for serious adverse event

Any adverse event that:
- results in death; or
- is immediately life threatening; or
- requires inpatient hospitalisation; or
- requires prolongation of existing hospitalisation or
- results in persistent or significant disability/incapacity.

Health economic analysis

A cost-effectiveness analysis will be conducted to evaluate the rehabilitation programme. Participants' health-related quality of life will be incorporated through use of the SF6D utility index derived from the SF-36 v2.[52] Costs of the rehabilitation programme will be estimated based on the study protocol and budget. Cost associated with average weekly informal and formal carer hours required for activities of daily living and transport and new personal equipment purchased during the trial period will be estimated via participant self-report at each assessment. All items will be allocated a unit cost based on average costs or minimum wage for informal carer hours. An incremental cost per QALY for the intervention group relative to control will be reported. Extensive one way and probabilistic sensitivity analyses will be conducted.

Patient and public involvement statement

The research question was partially informed by patients' priorities expressed in a recent public forum hosted by the Friedreich's Ataxia Research Alliance, Muscular Dystrophy Association, National Ataxia Foundation and

Cure FA Foundation, entitled 'Voice of the patient', held on 2 June 2017 in the USA to inform the US Food and Drug Administration. Individuals with Friedreich ataxia expressed that specific treatments aimed at balance, mobility and dexterity were a 'great unmet need'. The intervention employed in this study is based on our pilot study examining rehabilitation for individuals with Friedreich ataxia.[14] Feedback on the intervention was collected from the participants enrolled and incorporated into this trial. Participants are not directly involved in recruitment; however, Australian ataxia support groups will distribute information on the study to their members. Patients and the public will not be involved in the conduct of the study. The burden of the rehabilitation programme and standard care will be assessed fortnightly throughout the trial. Individuals withdrawing from the study will have their reasons for withdrawal documented. A written summary of the results will be disseminated to participants at the end of the study. Following their enrolment in the trial, participants can request to receive a copy of their assessments if required for allied health or medical interventions.

Data collection and management

Data collection and storage

The study will use the REDCap database for data tracking and collection. A unique identifier will be allocated to all enrolled participants. This code and identifying data will be kept in the REDCap database, only accessible to the investigators listed on the approved protocol. The database will be set up to restrict exporting of identifying data. Primary information will be entered onto paper-based case report rorms (CRFs) by the investigators at each site. The CRFs will be stored in a locked filing cabinet in a locked office at each site.

Monitoring

Potential errors in the data will be identified via visual review, electronic edit check and data frequency reports. Apparent errors requiring action will be entered into data clarification worksheets and sent to the site principal investigator for consideration of corrections to the CRF or database. Completed worksheets will be signed by an investigator from the relevant site to verify that they have reviewed the queries and made any corrections. A record of all queries and corrections will be maintained.

Study monitoring

A data monitoring committee is not required for this study and there will be neither interim analyses nor stopping guidelines. This is due to the low risk nature of the intervention.[53] To monitor adverse events, all participants will be asked: 'how have you felt since our last conversation?', 'have you experienced any adverse events?' and 'have you used any new medications or changed your medication regime?'. The physiotherapist will record all adverse events including: adverse event description; onset date, duration, date of resolution; severity; seriousness; any action taken; outcome and the likelihood of a causal relationship to the study treatment. Serious adverse events will be reported to the Human Research Ethics Committees and all the principal investigators by the chief investigator. An audit of study processes and data collection will occur at least once at each site.

Ethics and dissemination

The study has obtained approval from the Monash Health Human Research Ethics Committee (HREC) (reference number: HREC/18/MonH/418) and the HREC of the Northern Territory Department of Health and Menzies School of Health Research (reference number: 2019/3503). Postapproval protocol modifications will be resubmitted to the HRECs and communicated to site principal investigators. This study was registered prospectively with the Australian and New Zealand Clinical Trials Registry on 30 May 2018 (Universal Trial Number U111-1214-2471).

There are minimal safety considerations in this trial. Risks associated with participation in the rehabilitation programme are consistent with the risks in clinical practice and are mitigated by the level of support provided by the physiotherapist and the individualised nature of the rehabilitation. If any harm arises as a result of the study treatment, participants will be assisted with arranging appropriate medical treatment.

Sharing of data will follow the National Health and Medical Research Council principles for accessing and using publicly funded data for health research. Non-identifiable data may be shared for related research. Any peer-reviewed publications will be made openly accessible in an institutional repository (dependent on journal copyright restrictions). The metadata will be made openly accessible through the Murdoch Children's Research Institute. Murdoch Children's Research Institute will maintain custody of the central database.

All involved sites will be acknowledged in research outputs. The findings of this research will be submitted for peer-reviewed publication and presented at international or national conferences.

Protocol version

The study protocol was approved on 08 August 2018. The present manuscript details the latest version of the protocol (V.8) approved on 12 February 2020.

Study status

Recruitment of participants was initiated in December 2018. Forty-two participants have been enrolled in the study. Participant recruitment is anticipated to finish in 2022.

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Contributors SCM, LAC and MBD conceived and designed the study. DS, JB and CL contributed to the design of the study. SCM, MR, JC, SW and ACGrootendorst contributed to detailed description of the intervention. ACGrobler is the senior statistician in this trial and contributed to the design, randomisation and statistical analysis. LM, ACGrootendorst, LW and DL designed a preliminary, formative research study required for increased engagement and participation by Indigenous Australians in this trial. KD designed the economic analysis. SCM drafted the manuscript. SCM, LAC, MR, DS, JB, ACGrobler, SW, JC, CL, PJL, ACGrootendorst, LM, CS, KD, DL, LW, AF, PG and MBD contributed to the establishment of the protocol, revised the manuscript and provided input according to their area of expertise.

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Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

Kingston Centre

Title	The efficacy of rehabilitation for hereditary cerebellar ataxia. A randomised controlled trial.
Short Title	Rehabilitation for ataxia trial
Protocol Number	Version 7. 13/11/2019
Coordinating Principal Investigator/ Principal Investigator	Dr Sarah Milne Ms Melissa Roberts
Associate Investigator(s)	Professor Martin Delatycki Ms Shannon Williams (Perth) Ms Jillian Chua (Sydney) Ms Alison Grootendorst (Darwin) Ms Aleka Freijah (Darwin) Dr Louise Corben Dr Phillipa Lamont Dr David Szmulewicz Prof Joshua Burns Prof Carolyn Sue Dr Christina Liang Ms Libby Massey Mr Paul Gerken
Location	Kingston Centre, Monash Health

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project. This is because you have been diagnosed with a genetic ataxia. The research project is testing the effects of physical rehabilitation for people with hereditary cerebellar ataxia.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatment involved. Knowing what is involved will help you decide if you want 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 to take part, you might want to talk about it with a relative, friend or your local doctor. If you require an interpreter, please ask the study doctor and you will be provided with an interpreter to explain this research study and the information on this form.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want 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 take part in the research project
• Consent to have the tests and treatments that are described
• Consent to the use of your personal and health information as described.

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

2 What is the purpose of this research?

Aims and objectives of the project: This project aims to examine whether six weeks of outpatient rehabilitation followed by a 24-week home exercise program with fortnightly support from a physiotherapist will improve the ability to move and function in everyday activities. This project will compare the effectiveness of this program with the effectiveness of the therapy or exercise people are currently completing.

Background: A recent review of all available research found that rehabilitation for people with ataxia improves balance, the ability to function and walking speed. However, published studies are mainly based on very small numbers of people and have used methods that don't provide conclusive evidence. Studies have also shown that the benefits from attending outpatient rehabilitation are difficult to maintain.

Justification and significance of the project: This study is aims to determine if outpatient rehabilitation and home exercises can improve physical ability, balance and ataxia symptoms. It aims to recruit 80 people with ataxia across Australia. The findings from this study will guide services, clinicians and individuals with ataxia in deciding on the most appropriate therapy for people with a genetic ataxia.

This research has been initiated by the study doctors, Prof Martin Delatycki and Dr Sarah Milne.

This research has been funded by a National Health and Medical Research Council (NHMRC) Medical Research Future Fund Lifting Clinical Trials and Registries Capacity Grant.

This research is being conducted by researchers at the Murdoch Children's Research Institute, Monash Health, Alfred Health, Royal Perth Hospital, Sir Charles Gairdner Hospital, Royal North Shore Hospital, Ryde Hospital, Royal Darwin and Palmerston Regional Hospitals, and the MJD Foundation.

3 What does participation in this research involve?

Consent: If you are willing to participate, you will be asked to sign this consent form to indicate that you wish to participate in the study. No research will be conducted unless your consent is provided, and you are willing to participate.

Screening for participation in the project: People who have a diagnosis of hereditary cerebellar ataxia and who attend the Neurogenetic or Ataxia Clinics at Monash Medical Centre, Caulfield Hospital, Royal Children's Hospital, Royal Melbourne Hospital, Royal Perth Hospital, Royal North Shore Hospital Royal Darwin and Palmerston Hospitals and the MJD Foundation will be screened by their physiotherapist or neurologist to determine if they may be eligible to participate. They will be asked to attend an initial appointment to discuss the study and sign this

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consent form. For some people, this may involve a consultation with a neurologist to confirm their diagnosis and establish a medical contact for the duration of the study. All people meeting the eligibility criteria will be given the opportunity to participate in the project.

Random allocation: If you are willing to participate, you will be randomly allocated to an intervention group or a control group. The intervention group will be provided with a six-week outpatient rehabilitation program followed by a 24-week home exercise program with alternating fortnightly home visits and a video or phone call from a physiotherapist to support you complete the program. The control group will be asked to maintain their current physiotherapy or exercise program for 30 weeks.

This is a randomised controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance (random). You have a one in two chance you will receive the rehabilitation intervention in this study, and a one in two chance you will receive no intervention.

Participation for the intervention group: If you are allocated to the intervention group, you will be asked to attend a structured rehabilitation program and four assessment sessions at the Kingston Centre, Cheltenham.

The rehabilitation will involve outpatient physiotherapy three times per week for six weeks. Each session of rehabilitation will consist of two hours of physiotherapy: one hour of physiotherapy on land and one hour of physiotherapy in a hydrotherapy pool. A physiotherapy assistant will support the physiotherapist. Your program will be focused on improving your physical function and you can set personal goals in conjunction with the physiotherapist. The program will target balance, co-ordination, core-stability, daily function and strength. After the six-week outpatient rehabilitation program, you will be provided with a home exercise program. You will be asked to complete the home program for one hour, five days per week, for 24-weeks. Your home exercise program will involve fortnightly physiotherapy support. This will be through alternating home visits and video calls. The physiotherapist will modify and progress your home exercise program and provide you with encouragement to continue the program.

If you are allocated to the intervention group, you will be asked to attend four, two-hour assessment sessions. At these sessions you will be required to undergo a physical exam of co-ordination, sensation, balance and walking or sitting. You will also be asked questions about your quality of life, your independence in completing daily activities and the amount of exercise you are completing. If you can walk, you will also be instructed to wear a Fitbit for seven consecutive days once you have returned back home. The Fitbit is worn on your wrist and contains sensors that will measure the number of steps taken. You will be required to complete this activity during your normal day to day routine. The four assessment sessions will occur: at the beginning of the study, after 6 weeks, 18 weeks and 30 weeks.

Participation for the control group: If you are allocated to the control group, you will be asked to continue the same amount of exercise and/or therapy you were doing when you commenced the study. You will be asked to continue this for 30-weeks. You will also be asked to attend four assessment sessions at the Kingston Centre, Cheltenham.

If you are allocated to the control group, you will be asked to attend four, two-hour assessment sessions. At these sessions you will be required to undergo a physical exam of co-ordination, sensation, balance and walking or sitting. You will also be asked questions about your quality of life, your independence in completing daily activities and the amount of exercise you are

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completing. If you can walk, you will also be instructed to wear a Fitbit for seven consecutive days once you have returned back home. The Fitbit is worn on your wrist and contains sensors that will measure the number of steps take. You will be required to complete this activity during your normal day to day routine. The four assessment sessions will occur: at the beginning of the study, after 6 weeks, 18 weeks and 30 weeks.

Video recording: We will ask up to 20 adult participants permission to record their first assessment with a video recorder. This will be used by the principal investigator to train all the physiotherapists who are completing the assessments. This is to ensure their assessments are accurate and consistent. We may also ask adult participants in the rehabilitation group permission to record one treatment session with a video recorder. This will be used by principle investigator to work with the other physiotherapists to ensure the treatments are consistent and best practice across the sites.

Limiting bias: This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids chief investigators or participants jumping to conclusions.

If you participate in the study, you will be asked not to discuss the group you have been allocated to during your assessment with the physiotherapist. This ensures the assessing physiotherapist is not biased when he/she assesses you.

Costs and reimbursement: There are no additional costs associated with participating in this research project, nor will you be paid. All tests and physiotherapy care required as part of the research project will be provided to you free of charge. You will be reimbursed for any reasonable travel and parking associated with the research project visit.

GP information: It is desirable that your local doctor be advised of your decision to participate in this research project if you are allocated into the rehabilitation group. If you have a local doctor, we recommend that you inform them of your participation in this research project.

4 What do I have to do?

It is important to tell the research staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments.

You are unable to participate in this study if you are already participating or plan to participate in any drug trials during the 30-weeks you are participating in this study.

There are no other restrictions for participating in this study.

5 Other relevant information about the research project

We plan to include 80 people with hereditary cerebellar ataxia in this project, both adults and children over 15 years of age.

We plan to include 40 people at this site, Kingston Centre, Cheltenham.

This project involves researchers from the Monash Health, Alfred Health, Royal Perth Hospital, Sir Charles Gairdner Hospital, Royal North Shore Hospital, Ryde Hospital, Royal Darwin and Palmerston Regional Hospital and Machado-Joseph Disease Foundation Offices, Coconut

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Grove and Groote Eylandt working in collaboration with the researchers at the Murdoch Children's Research Institute.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Monash Health or Alfred Health.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at this hospital. Other options are available; these include accessing physiotherapy or similar services such as exercise physiology in the community. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, if you are allocated to the intervention group possible benefits may include an improvement in strength and balance.

If you are allocated to the control group there will be no clear benefit to you from your participation in this research.

However, there are potential indirect benefits. This study will hopefully result in a better understanding of the effects of outpatient rehabilitation and supported home exercise in people for genetic ataxia. This will guide for clinicians who provide care to people with ataxia and will provide justification for rehabilitation care.

9 What are the possible risks and disadvantages of taking part?

While there are no obvious risks from participation in this study, possible risks could include fatigue from attending rehabilitation and an increased risk of falling due to fatigue and challenging balance.

This will be monitored by the researcher and the physiotherapist and rest breaks and the therapy provided will be modified accordingly. Please discuss any concerns with the researcher.

If you become upset or distressed as a result of your participation in the research, the study doctor will be able to arrange for counselling or other appropriate support.

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10 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, your study doctor will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

11 Can I have other treatments during this research project?

It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project.

12 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any concerns you may have, or special requirements related to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

13 Could this research project be stopped unexpectedly?

This research project will not be stopped unexpectedly.

14 What happens when the research project ends?

If you wish to know the results of this research project once it has been completed, we would be happy to send you a letter explaining our overall findings.

Part 2 How is the research project being conducted?

15 What will happen to information about me?

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By signing the consent form, you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential.

Hard copy data will be stored in a locked cabinet and securely stored at the Kingston Centre. You will be allocated a non-identifiable code for the purpose of analysing the results. Your data, including your name and date of birth, will be entered into a password protected database at the Murdoch Children's Research Institute, Melbourne. Only the research team listed in this form will have access to this information. The database will be set up so that your personal details cannot be exported.

If you agree to a recording of your assessment, the video of your assessment will only be shared with other researchers listed on this form, for the purpose of this research. The video will be stored for a minimum seven years on a password protected computer and will be permanently destroyed at this time.

Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form, you agree to the study team accessing health records if they are relevant to your participation in this research project. This will include obtaining your genetic test results for the purpose of confirming your diagnosis and the genetic variation that resulted in your diagnosis.

Your health records and any information obtained during the research project are subject to inspection for the purpose of verifying the procedures and the data. This review may be done by the study sponsor, Murdoch Children's Research Institute or the institution relevant to this Participant Information Sheet, Monash Health, or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant research personnel and regulatory authorities as noted above.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified, except with your permission. Confidentiality will be maintained as data will presented as a group in any publication/presentation arising from this project. Individual data will not be identifiable.

In accordance with relevant Australian and Victorian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

Future research: The Murdoch Children's Research Institute are the custodians of the database and may share this data with other researchers after completion of the study. This data will be non-identifiable and will not be able to identify you. Your information will be stored on the database for use only in future research studies that are related to the original research project.

Any information obtained for the purpose of this research project *and for the future research described in Section 16* that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

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16 Injury

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

17 Who is organising and funding the research?

This research project is being conducted by Professor Martin Delatycki and Dr Sarah Milne.

Funding is provided by a National Health and Medical Research Council, Medical Research Future Fund grant. The Murdoch Children's Research Institute is administering the funds for this research project.

Monash Health will receive a payment from Murdoch Children's Research Institute for undertaking this research project.

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

18 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 Monash Health.

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.

19 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project, you can contact the principal study doctor, Dr Sarah Milne on (03) 8341 6442, or any of the following people:

Clinical contact people

Name	*Professor Martin Delatycki*
Position	*Friedreich Ataxia Clinic Director*
Telephone	(03) 8341 6290

For matters relating to research at the site at which the participant is taking part, the details of the local site complaints person are:

Complaints contact person

Name	*Deborah Dell*
Position	*Manager, Human Research Ethics Committees*
Telephone	(03) 9594 4611
Email	*Deborah.dell@monashhealth.org*

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	Monash Health
HREC Executive Officer	*Deborah Dell*
Telephone	(03) 9594 4611
Email	*Deborah.dell@monashhealth.org*

Local HREC Office contact (Research Governance Officer)

Name	Michael Kios
Position	Research Governance Officer
Telephone	(03) 9594 4606
Email	michael.kios@monashhealth.org

Consent Form - *Adult providing own consent*

Title	The efficacy of rehabilitation for hereditary cerebellar ataxia. A randomised controlled trial.
Short Title	Rehabilitation for ataxia trial.
Protocol Number	Version 7. 13/11/2019
Coordinating Principal Investigator/ Principal Investigator	Dr Sarah Milne Ms Melissa Roberts
Associate Investigator(s)	Professor Martin Delatycki Ms Shannon Williams Ms Jillian Chua Ms Alison Grootendorst Ms Aleka Freijah Dr Louise Corben Dr Phillipa Lamont Dr David Szmulewicz Prof Joshua Burns Prof Carolyn Sue Dr Christina Liang Ms Libby Massey Mr Paul Gerken
Location	Kingston Centre, Monash Health.

Consent Agreement

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 my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to Murdoch Children's Research Institute concerning my disease and treatment 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 participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

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

Declaration by Participant – for participants who have read the information

Name of Participant (please print) _____

Signature _____ Date _____

Declaration – for participants unable to read the information and consent form

Witness to the informed consent process

Name (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project; its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

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

By signing this consent section, I consent to the storage of my de-identified information on the database managed by the Murdoch Children's Research Institute, as described in *section 15*, for any related future research. By signing this consent form, I agree to the use of my information for the purposes of any further research related to this project.

Yes ☐ No ☐

Declaration by Participant – for participants who have read the information

Name of Participant (please print) _____

Signature _____ Date _____

Declaration – for participants unable to read the information and consent form

Witness to the informed consent process

Name (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

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

By signing this consent section, I consent to my first assessment session to be recorded, for the purposes of this research project only. By signing this consent form, I agree this video to be shared with other researchers listed on this protocol.

Yes ☐ No ☐

Declaration by Participant – for participants who have read the information

Name of Participant (please print) _____

Signature _____ Date _____

Declaration – for participants unable to read the information and consent form

Witness to the informed consent process

Name (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

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

By signing this consent section, I am willing to be contacted by the researchers named in this study about future research for which I may be eligible. I understand I am under no obligation to participate if contacted.

Yes ☐ No ☐

Declaration by Participant – for participants who have read the information

Name of Participant (please print) _____

Signature _____ Date _____

Declaration – for participants unable to read the information and consent form

Witness to the informed consent process

Name (please print) _____

Signature _____ Date _____

* Witness is not to be the investigator, a member of the study team or their delegate. In the event that an interpreter is used, the interpreter may not act as a witness to the consent process. Witness must be 18 years or older.

Declaration by Study Doctor/Senior Researcher†

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

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

Form for Withdrawal of Participation - *Adult providing own consent*

Title	The efficacy of rehabilitation for hereditary cerebellar ataxia. A randomised controlled trial.
Short Title	Rehabilitation for ataxia trial.
Protocol Number	Version 7. 13/11/2019
Coordinating Principal Investigator/ Principal Investigator	Dr Sarah Milne Ms Melissa Roberts
Associate Investigator(s)	Professor Martin Delatycki Ms Shannon Williams (Perth) Ms Jillian Chua (Sydney) Ms Alison Grootendorst (Darwin) Ms Aleka Freijah (Darwin) Dr Louise Corben Dr Phillipa Lamont Dr David Szmulewicz Prof Joshua Burns Prof Carolyn Sue Dr Christina Liang Ms Libby Massey Mr Paul Gerken
Location	Kingston Centre, Monash Health

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with Monash Health or Alfred Health.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

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

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

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

Appendix A: Treatment and exercise inventory - *Rehab for ataxia trial*

Exercises for rehabilitation outpatient and home-based intervention. Some exercises can be carried out in the hydrotherapy pool or on land, others are specific to the environment (i.e. turbulence – pool only).

Domain 1: Strengthening

Instructions:

A. Resistance may be applied through: 1) Gym equipment; 2) Theraband; 3) Free weights; 4) Therapist-applied; or 5) Pilates springs.
B. Strengthening may be focused on: 1) Eccentric control; 2) Repetition max dosage; 3) Movement quality (concentric control); 4) Movement quality and eccentric control; or 5) Eliciting contraction (for Oxford Grade 1+ and below muscle strength).
C. Strengthening may occur: 1) Throughout range of movement; or 2) Defined range of movement.
D. Facilitation includes: 1) Facilitation; 2) Support; 3) Modified Bad Ragaz method; 4) Turbulence (negative pressure - assistance) or 5) Assistance.

Below is the list of exercises that can be chosen for the *strengthening domain* (Table 1).

Table 1. Exercise List - Strengthening

Ankle plantarflexion	**Ankle dorsiflexion**	**Ankle inversion**	**Ankle eversion**
Ankle plantarflexion with buoyancy assistance	**Ankle dorsiflexion with buoyancy assistance**	**Ankle inversion with buoyancy assistance**	**Ankle eversion with buoyancy assistance**
Ankle plantarflexion with facilitation	**Ankle dorsiflexion with facilitation**	**Ankle inversion with facilitation**	**Ankle eversion with facilitation**
Ankle plantarflexion with resistance	**Ankle dorsiflexion with resistance**	**Ankle inversion with resistance**	**Ankle eversion with resistance**
Ankle plantarflexion with turbulence	**Ankle dorsiflexion with turbulence**	**Ankle inversion with turbulence**	**Ankle eversion with turbulence**
Knee flexion	**Knee extension**	**Hip abduction**	**Hip adduction**
Knee flexion with buoyancy assistance/resistance	**Knee extension with buoyancy assistance/resistance**	**Hip abduction with buoyancy assistance/resistance**	**Hip adduction with buoyancy assistance/resistance**
Knee flexion with facilitation	**Knee extension with facilitation**	**Hip abduction with facilitation**	**Hip adduction with facilitation**
Knee flexion with resistance	**Knee extension with resistance**	**Hip abduction with resistance**	**Hip adduction with resistance**
Knee flexion with turbulence	**Knee extension with turbulence**	**Hip abduction with turbulence**	**Hip adduction with turbulence**
Hip flexion	**Hip extension**	**Hip internal rotation**	**Hip external rotation**
Hip flexion with buoyancy assistance/resistance	**Hip extension with buoyancy assistance/resistance**	**Hip internal rotation with buoyancy assistance/resistance**	**Hip external rotation with buoyancy assistance/resistance**
Hip flexion with facilitation	**Hip extension with facilitation**	**Hip internal rotation with facilitation**	**Hip external rotation with facilitation**
Hip flexion with resistance	**Hip extension with resistance**	**Hip internal rotation with resistance**	**Hip external rotation with resistance**
Hip flexion with turbulence	**Hip extension with turbulence**	**Hip internal rotation with turbulence**	**Hip external rotation with turbulence**
Hip-knee extension: Squats	**Hip-knee extension: Lunges**	**Hip-knee extension**	**Exercise Bike**
Running down stairs	**Bound down off step**	**Bounding**	**Hopping**
Skipping	**Scapular retraction**	**Scapular protraction**	**Shoulder IR**

Shoulder ER	**Shoulder flex**	**Shoulder ext**	**Shoulder elevation/depression**
Other			

Domain 2: Postural Control

Instructions:

A. Graded facilitation for all exercises to ensure quality movement using resistance, turbulence, buoyancy support, gravity support, equipment support and environment and facilitation techniques.

Below is the list of exercises that can be chosen for the *postural control domain* (Table 2).

Table 2. Exercise List – Postural Control

Pelvic ant/post tilt - sitting	**Four-point kneeling – cat/cow**	**Bridging with pelvic tilt**	**Seaweeding**
Pelvic ant/post tilt - lying	**Four-point kneeling – hip extension**	**Bridging with pelvic tilt –leg to side**	**Rot control in supine using buoyancy**
Pelvic ant/post tilt - standing	**Four-point kneeling – hip extension & arm raise**	**Bridging with pelvic tilt – leg lift**	**Fixed ULs with LL rot**
Pelvic ant/post tilt – 2-point kneeling	**Four-point kneeling – arm raise rot**	**Bridging with pelvic tilt – one leg off bed**	**Standing – reaching laterally with buoyancy**
Pelvic ant/post tilt – 4-point kneeling	**Four-point kneeling – arm raise**	**Single leg bridging**	**Standing – reaching rot with buoyancy**
Pelvic lateral tilt - sitting	**Four-point kneeling – arm raise**	**Bridging off fitball**	**Standing with UL movement – flex/ext bilat with buoyancy**
Pelvic lateral tilt - lying	**Two-point kneel- alternate legs through to lunge**	**Supine – LL rot on top of fitball**	**Standing with UL movement – flex/ext unilat with buoyancy**
Pelvic lateral tilt - standing	**Sitting – rolling down**	**Supine – hip/knee flex/ext on fitball**	**Standing with UL movement – rot unilat with buoyancy**
Thoracic flex/ext - sitting	**Sitting – rolling down with rot**	**Two-point kneel – rolling ball fwd/fwd**	**Standing with UL movement – rot bilat with buoyancy**
Thoracic flex/ext - lying	**Standing – rolling down**	**Supine – unilateral hip eccentric IR – opposing leg stable**	**Standing with UL resisted movement – flex/ext bilat with buoyancy**
Thoracic flex/ext - standing	**Standing – rolling down with rot**	**Supine – unilateral hip ER with resistance – opposing leg stable**	**Standing with UL resisted movement – flex/ext unilat with buoyancy**
Sit-ups	**Supine balance on roll, knees bent**	**Sidelying hip ER**	**Standing with UL resisted movement – rot unilat with buoyancy**
Sit ups with rot	**Supine balance on roll, knees bent with unilateral shoulder horizontal extension**	**Sidelying hip ER with resistance**	**Standing with UL resisted movement – rot bilat with buoyancy**
Standing – reaching laterally	**Sitting – reaching laterally**	**Sidelying hip ER + IR**	**Standing – reaching laterally with turbulence**
Standing – reaching rot	**Sitting – reaching rot**	**Sidelying hip ER +IR with resistance**	**Standing – reaching rot with turbulence**
Standing with UL movement – flex/ext bilat	**Sitting with UL movement – flex/ext bilat**	**Prone thoracic extension**	**Standing with UL movement – flex/ext bilat with turbulence**
Standing with UL movement – flex/ext unilat	**Sitting with UL movement – flex/ext unilat**	**Prone cervical retraction**	**Standing with UL movement – flex/ext unilat with turbulence**

Standing with UL movement – rot unilat	**Sitting with UL movement – rot unilat**	**Sitting cervical retraction**	**Standing with UL movement – rot unilat with turbulence**
Standing with UL movement – rot bilat	**Sitting with UL movement – rot bilat**	**Sitting cervical retraction – resistance into wall**	**Standing with UL movement – rot bilat with turbulence**
Standing with UL resisted movement – flex/ext bilat	**Sitting with UL resisted movement – flex/ext bilat**	**Downward facing dog**	**Standing with UL resisted movement – flex/ext bilat with turbulence**
Standing with UL resisted movement – flex/ext unilat	**Sitting with UL resisted movement – flex/ext unilat**	**Side plank**	**Standing with UL resisted movement – flex/ext unilat with turbulence**
Standing with UL resisted movement – rot unilat	**Sitting with UL resisted movement – rot unilat**	**Side plank with leg movement**	**Standing with UL resisted movement – rot unilat with turbulence**
Standing with UL resisted movement – rot bilat	**Sitting with UL resisted movement – rot bilat**	**Side plank with rot**	**Standing with UL resisted movement – rot bilat with turbulence**
Scapular retraction	**Scapular protraction**	**Prone standing – hip extension**	**Should IR**
Shoulder ER	**Shoulder flex**	**Shoulder ext**	**Shoulder elevation/depression**
Supine in pool reaching laterally/rotational control	**Bilat hip/knee flex/ext while standing on noodle in pool**	**Supine, unilateral hip and knee ext/flx from flexed position - opposing leg stable**	**Other**

Legend: UL = upper limb; LL = lower limb; ant = anterior; post = posterior; unilat = unilateral; bilat = bilateral; flex = flexion; ext = extension; IR: internal rotation; ER: external rotation; fwd = forward; bwd = backward; rot = rotation.

Domain 3: Functional Mobility

Instructions:

A. Facilitated movement may be: 1) Facilitated; or 2) Supported.
B. Resistance may be through: 1) Therapist-applied; 2) Theraband; or 3) Free weights.

Below is the list of exercises that can be chosen for the *functional mobility domain* (Table 3).

Table 3. Exercise List – Functional mobility

Bridging practice	**Rolling practice**	**Sideways walking with turbulence**	**Sitting-to-lying practice**
Facilitated bridging	**Facilitated rolling**	**Lying-to-sit practice**	**Facilitated sitting-to-lying**
	Rolling practice with buoyancy support	**Facilitated lying-to-sit**	**Sitting-to-lying practice with buoyancy support**
Sit-to-stand practice	**Gait practice**	**Lying-to-sit practice with buoyancy support**	**Forwards walking**
Sit-to-stand practice with resistance	**Facilitated gait**	**Part-practice gait**	**Forwards walking with facilitation**
Sit-to-stand practice with buoyancy support	**Gait practice with buoyancy support**	**Facilitated part-practice gait**	**Forwards walking with buoyancy support**
Sit-to-stand practice with turbulence	**Gait practice with resistance**	**Part-practice gait with buoyancy support**	**Forwards walking with resistance**
Backwards walking	**Gait practice with turbulence**	**Turning practice**	**Forwards walking with turbulence**
Backwards walking with facilitation	**Sideways walking**	**Turning practice with buoyancy support**	**Stairs practice**
Backwards walking with buoyancy support	**Sideways walking with facilitation**	**Turning practice with turbulence**	**Facilitated stairs**
Backwards walking with resistance	**Sideways walking with buoyancy support**	**Walking in dynamic environment**	**Stairs practice with buoyancy support**

Backwards walking with turbulence	**Sideways walking with resistance**	**Walking with randomly prompted sudden directional changes**	**Stairs practice with turbulence**
Walking with randomly cued sudden stopping	**Walking with randomly cued head direction changes**	**Running**	**Floor transfers**
Step ups/ downs with rotation	**Walking stepping up and down curb**	**Walking on uneven surfaces with supervision**	**Other**

Domain 4: Balance training

Instructions:

A. Unpredictable movement may be: 1) Pilates springs or 2) Throwing and catching.
B. Controlled movement may be: 1) Free range of movement; or 2) Theraband resistance.

Below is the list of exercises that can be chosen for the *balance domain* (Table 4).

Table 4. Exercise List - Balance

Static sitting balance	**Wobble board lateral**	**Standing balance single leg with reaching to the floor and return**
Static sitting balance with eyes closed	**Wobble board anterior/posterior**	**Standing balance single leg with controlled lower limb movement**
Sitting balance with neck rotation	**Wobble board round**	**Standing balance single leg with unpredictable lower limb movement**
Sitting balance with trunk rotation	**Static standing balance step stance**	**Standing balance single leg with resisted lower limb movement**
Sitting balance with controlled upper limb movement	**Static standing balance tandem stance**	**Tandem walking**
Sitting balance with unpredictable upper limb movement	**Static standing balance step stance eyes closed**	**Sideways walking**
Sitting balance with resisted upper limb movement	**Static standing balance tandem stance eyes closed**	**Forward walking**
Sitting balance with reaching to the floor and return	**Static standing balance step stance on foam**	**Backwards walking**
Sitting balance with controlled lower limb movement	**Static standing balance tandem stance on foam**	**Half-rotation step**
Sitting balance with unpredictable lower limb movement	**Standing balance step stance with neck rotation**	**Turning practice**
Sitting balance with resisted lower limb movement	**Standing balance tandem stance with neck rotation**	**Stepping up/down step**
Static standing balance feet apart	**Standing balance step stance with trunk rotation**	**Side stepping up/down step**
Static standing balance feet together	**Standing balance tandem stance with trunk rotation**	**Step taps plus variations**
Static standing balance feet apart eyes closed	**Standing balance step stance with controlled upper limb movement**	**Weaving in/out of cones**
Static standing balance feet together eyes closed	**Standing balance tandem stance with controlled upper limb movement**	**Stepping over obstacles**
Static standing balance feet apart on foam	**Standing balance step stance with unpredictable upper limb movement**	**Walking on soft mat**
Static standing balance feet together on foam	**Standing balance tandem stance with unpredictable upper limb movement**	**Sit-to-stand**
Standing balance feet apart with neck rotation	**Standing balance step stance with resisted upper limb movement**	**Half sit-to-stand**
Standing balance feet together with neck rotation	**Standing balance tandem stance with resisted upper limb movement**	**Balancing on toes**

Standing balance feet apart with trunk rotation	**Standing balance step stance with reaching to the floor and return**	**Heel-raises**
Standing balance feet together with trunk rotation	**Standing balance tandem stance with reaching to the floor and return**	**Squats**
Standing balance feet apart with controlled upper limb movement	**Static standing balance single leg**	**Lunges**
Standing balance feet together with controlled upper limb movement	**Static standing balance single leg eyes closed**	**Weight-shifting in standing**
Standing balance feet together with unpredictable upper limb movement	**Static standing balance single leg on foam**	**Sit-to-stand plus one step**
Standing balance feet apart with resisted upper limb movement	**Standing balance single leg with neck rotation**	**Sitting balance on fitball**
Standing balance feet apart with unpredictable upper limb movement	**Standing balance single leg with trunk rotation**	**Sitting balance on fitball – alternate leg lift**
Standing balance feet together with resisted upper limb movement	**Standing balance single leg with controlled upper limb movement**	**Grapevine walking**
Standing balance feet apart with reaching to the floor and return	**Standing balance single leg with unpredictable upper limb movement**	**Standing and reaching**
Standing balance feet together with reaching to the floor and return	**Standing balance single leg with resisted upper limb movement**	**Sitting and reaching**
Walking with randomly prompted sudden directional changes	**Walking with randomly cued sudden stopping**	**Walking with randomly cued head direction changes**
Balancing on pool equipment	**Throwing/catching**	**Standing balance single leg with hip rotation- step over imaginary objects or up onto step**
Big stepping to targets slow, fast and unpredictable	**Backwards walking obstacle course**	**Other**

Domain 5: Coordination and Control Exercises

Instructions:

A. Concentrate on eccentric control and multi-joint facilitated exercises.

B. Use targets to direct movement

C. Use facilitation, resistance, verbal prompts if required

Below is the list of exercises that can be chosen for the *co-ordination and control domain* (Table 5).

Table 5. Exercise List – Coordination and control

Ankle dorsiflexion with facilitation	**Ankle inversion with facilitation**	**Ankle eversion with facilitation**	**Facilitated ankle plantarflexion in lying**
Ankle dorsiflexion with turbulence	**Ankle inversion with resistance**	**Ankle eversion with resistance**	**Facilitated ankle plantarflexion in sitting**
Facilitated ankle dorsiflexion with lengthening of the soleus muscle	**Ankle inversion and hip adduction with resistance**	**Ankle eversion and hip abduction with resistance**	**Facilitated ankle plantarflexion in standing - bilateral**
Knee extension with buoyancy assistance	**Hip abduction with buoyancy assistance**	**Hip adduction with buoyancy assistance**	**Facilitated ankle plantarflexion in standing - unilateral**
Knee extension with facilitation	**Hip abduction with facilitation**	**Hip adduction with facilitation**	**Supine – unilateral hip eccentric IR – opposing leg stable**
Hip extension with buoyancy assistance	**Hip internal rotation with buoyancy assistance**	**Hip external rotation with buoyancy assistance**	**Supine – unilateral hip ER with resistance – opposing leg stable**

Hip extension with facilitation	**Hip internal rotation with facilitation**	**Hip external rotation with facilitation**	**Sidelying hip ER**
Knee extension with facilitated hamstring lengthening	**Sit-to-stand with theraband to increase hip ER activity**	**Squats with theraband to increase hip ER activity**	**Sidelying hip ER with resistance**
Hip-knee extension: Lunges - facilitated	**Alternate hip/knee flexion/extension on pilates table**	**Facilitated shoulder protraction-retraction**	**Sidelying hip ER + IR**
Hip-knee extension: Leg press - facilitated	**Exercise Bike**	**Ballistic mini tramp alternate ankle dorsiflexion/plantar flexion**	**Sidelying hip ER +IR with resistance**
Bounding	**Grapevine walking**	**Skipping**	**Switch lunges**
Supine unilateral hip/knee extension +/- alternate legs	**Stepping to targets**	**Step taps plus variations**	**Passing ball around legs/trunk**
Unilateral hip/knee extension on fit ball	**Unilateral hip/knee extension on pool noodle**	**Throw and catch with 360° turns**	**Catching with step lunge unpredictable**
Other			

Legend: ER = external rotation; IR = internal rotation.

Domain 6: Sensory stimulation, mobilisation and stretching, and vestibular rehabilitation

Instructions:

The aim of stretching, mobilising and sensory stimulation is to allow functional retraining and strengthening in the most beneficial position. Therefore, these exercises/techniques should occur prior to the active activity aimed for (i.e. calf stretch for part-practice gait focusing on terminal phase of stance).

Below is the list of exercises that can be chosen for the *Sensory stimulation, mobilisation and stretching domain* (Table 6).

Table 6. Exercise List - Sensory stimulation, mobilisation and stretching

Closed-chain metatarsophalangeal flexion practice	**Ankle inversion with resistance.**	**Soft-tissue massage of the gastrocnemius**
Closed-chain metatarsophalangeal flexion facilitation	**Ankle eversion with resistance.**	**Soft-tissue massage of the soleus**
Phalangeal flexion – all toes practice	**Calf raises with eccentric lengthening practice**	**Soft-tissue massage of the foot.**
Phalangeal flexion – all toes facilitation	**Calf raises with eccentric lengthening with facilitation**	**Static gastrocnemius stretching in standing.**
Interphalangeal joint flexion – isolated toes practice	**Static hip adductor stretch in lying**	**Static gastrocnemius stretching in lying.**
Interphalangeal joint flexion – isolated toes facilitation	**Thoracic rotation stretch in sitting**	**Static gastrocnemius stretching in lying, with therapist**
Pick up small objects with toes practice	**Thoracic rotation stretch in lying**	**Static soleus stretching in sitting.**
Selective toe metatarsophalangeal flexion practice	**Static psoas stretch in lying with therapist**	**Static soleus stretching in sitting, with therapist**
Selective toe metatarsophalangeal flexion facilitation	**Static psoas stretch in lying**	**Static soleus stretching in standing.**
Facilitated first toe circumduction	**Static psoas stretch in standing**	**Static tibialis anterior stretch in sitting**
Facilitated fifth toe circumduction.	**Static hip adductor stretch in lying with therapist**	**Static tibialis anterior stretch in sitting with therapist**
Facilitated ankle dorsiflexion with lengthening of the soleus muscle, with subtalar joint accessory movements	**Latissimus dorsi stretch**	**Accessory movements of metatarsal bones**
Facilitated ankle dorsiflexion with lengthening of the soleus muscle,	**Soft-tissue massage of psoas**	**Accessory movements of the subtalar joint**

without subtalar joint accessory movements		
Lateral flexion trunk	**Soft-tissue massage of adductors**	**Thoracic mobilisations**
Rotation of trunk	**Soft-tissue massage pectorals**	**Thoracic mobilisations with buoyancy**
Gaze stabilization in sitting	**Gaze stabilization in standing feet apart**	**Other**

Appendix B: Rehabilitation program – additional guidance for clinical reasoning and physiotherapy approach.

1. Clinical assessment

The physiotherapist will assess each individual at the beginning of the intervention to ensure the chosen therapy options are appropriate for (i) the participant's capacity and impairments; (ii) the environment of the home exercise program (HEP); (iii) the specific needs of each participant; and (iv) the feasibility of successfully delivering the rehabilitation at that site.

To assist with this the physiotherapist should:

- Review the Baseline Assessment completed by the blinded assessor.
- Complete the Assessment Form, including developing three goals using the Goal Attainment Scale(1).
- Assess 6-15 repetition max (RM) weakened muscles that will be a focus of the strengthening component of the rehabilitation.

The three functional goals determined by the participant and the assessment findings should be used to individualise the rehabilitation program to the participant's specific needs.

2. Clinical reasoning

Considerations to assist with clinical reasoning and the physiotherapy program include:

- Consider order of exercises and focus on controlled movement with correct posture/form where possible.
- If hands on facilitation required for correct posture or facilitation of movement, aim to decrease this over outpatient program.
- Review goals and impairments weekly.
- Determine action plan to achieve goals and address impairments (record weekly).
- Each week review program and consider the following:
    - fatigue levels
    - progression of performance
    - progression to goals
    - variability of training
    - progressive resistance training protocol
    - participant motivation.
- Follow clinical reasoning considerations for each domain as below.
- Document rationale for progression/change.

3. Outpatient rehabilitation intervention

Considerations to assist with the outpatient program, scheduling and monitoring include:

- Choose exercises from Appendix A - Exercise List or add in exercises into the appropriate domain if they are not already included.
- Scheduling:
    - The outpatient program consists of two hours, three days per week for six weeks.
    - Please consider the following if there is a need to reschedule any sessions within the six weeks:
        - You cannot split the two-hour session into two one-hour sessions. If the participant is only able to attend half a session, please document as did not attend (DNA) for that half session.
        - You can reschedule a two-hour session to an alternate day in the same week if feasible.
    - Aim, where possible, to have one break day between each session, but at least one break day per week must be incorporated as a minimum (so cannot run three days of rehab in a row).
- Review program weekly and re-visit clinical reasoning.
- Spend the correct time on each domain (Table 1).

Table 1. Time spent in each domain for outpatient rehabilitation program

	Domain	**Time per session**
(i)	Strengthening	35 minutes
(ii)	Postural control	20 minutes
(iii)	Functional mobility	20 minutes
(iv)	Balance Training	20 minutes
(v)	Coordination and control	15 minutes
(vi)	Sensory stimulation, mobilisation and stretching	10 minutes

- For the *Strengthening* domain review separate instructions and progress as recommended.
- Monitor fatigue, pain and falls at each visit (monitoring fortnightly).

- Progress the program according to the individual's performance of each exercise, their fatigue and motivation levels, and their goals.

3. Home exercise program

Considerations to assist with the HEP component and monitoring include:

- Devise HEP for first week during outpatient rehabilitation program.
- Assess and modify program at each visit/conference call.
- Program should be one hour, five times per week.
- Choose from Appendix A - Exercise List.
- Participant can use family/carer/therapist/fitness instructor can carry out the program if already available to the participant or initiated by the participant.
- Spend the correct time on each domain (Table 2).

Table 2. Time spent in each domain for outpatient rehabilitation program

	Domain	**Time per session**
(i)	Strengthening	15 minutes
(ii)	Postural control	10 minutes
(iii)	Functional mobility	10 minutes
(iv)	Balance Training	15 minutes
(v)	Coordination and control	5 minutes
(vi)	Sensory stimulation, mobilisation and stretching	5 minutes

- Each visit re-assessment key problem areas, progress on goals and identified impairments and review clinical reasoning.
- For the *Strengthening* domain review separate instructions and progress as recommended.
- Monitor fatigue, pain and falls at each visit.

5. Documentation

- Document exercises/therapy in program record.
- Document DNAs and adverse events.

- Document fatigue, pain and falls in program record/monitor.
- Document reasons for progression.
- Collect participant's record of HEP once completed.

6. Clinical reasoning considerations for each domain

a) Strengthening domain

- Identify muscle weakness and address through progressive resistance training procedure (details under Point 8 below).
- Target key areas of impairment and limitations to function/goals primarily.
- Consider during each program when to complete the strengthening component. For example: completed at the beginning may increase load used; completed at the end may allow the other domains to be performed when the muscles are not fatigued; or completed throughout may enhance muscle recovery.
- Consider position of assessment and treatment to maximise strength gains and/or functional strength.

b) Postural control

- Identify areas to work on through observation during functional activities or planned exercises in other domains.
- Can use lying, sitting, standing, prone standing, wall standing, etc. to work on postural control with aim of working on selective control in a functional position (i.e. posterior/lateral pelvic tilt for single leg stance).
- Progress from working at level of control to increasing demands from gravity (consider position when completing the exercise)(2).
- May need to work on increasing available range of movement (ROM) prior to working on active movement control against gravity.
- Monitor and avoid trunk or upper limb fixation when performing stabilising trunk exercises.

c) Functional mobility

- Choose tasks that are related to participant goals or steps to achieving goals.
- Practice functional mobility after working on postural control or coordination and control domain exercises that are relevant to the task (e.g. to improve the postural control during that task).
- Practice functional mobility in the hydrotherapy pool to increase balance, strength and coordination demands or increase available ROM during functional activity safely (increasing speed of movement is helpful for this).

d) Balance

- Consider different surfaces to challenge balance.
- Increase speed of exercise as able.
- Use "hand's on" (the physiotherapist providing the stabilisation) and consider location of the body where support/stabilisation is provided, rather than asking the participant to use their upper limbs for stabilization/safety.
- Progress balance to outside of parallel bars where-ever possible and safe.
- If using pool environment, consider functional speed.

e) Coordination and control

- Start movements small and slow and progress to full ROM and fast as able to control.
- Consider required speed of functional movements when prescribing exercises.
- Incorporate eccentric control into exercises worked on in this domain.
- Consider error size for motor learning(3) - push into position of challenge, but with some ability to correct.
- Lots of repetition is important(2).
- Consider exercises that switch between agonist/antagonist concentric muscle activity.
- Consider multi-joint movement have a higher coordination-demand versus single-joint movements.
- Work in functional positions when possible, to improve functional carryover.

f) Sensory stimulation, mobilisation and stretching, and vestibular rehabilitation

- Focus on the foot and intrinsic muscles of the foot and ankle.
- Active activity of the foot is thought to provide greater proprioceptive input(4) so aim for this as able, as a component of this domain.
- If ROM limitations are identified, provide stretching/soft tissue work/mobilisation as required then incorporate changes into part-practice and full practice of functional activity or into strengthening of muscle through new ROM.
- Consider completing activities in barefoot to increase sensory input (where possible).
- It may be appropriate to target vestibular function (i.e. gaze stability(5)) in this domain if vestibular symptoms (such as visual fixation abnormalities(6)) have an impact on achieving participant goals or impact on ability to participate in the rehabilitation program.

7. Additional notes

- Patella-femoral joint pain can be an issue, potentially due to muscle imbalance/weakness. If this is present, hip external rotation activity during sit-to-stand practice and during any other knee work, may assist with this.

- Consider demand on muscles when working eccentrically. Monitor to avoid fatiguing during functional or multi-joint exercises.
- If participants ask for additional homework in between rehabilitation sessions or the structured HEP, this is okay. However, participants need to be prompted to include this extra work when completing the PhoneFITT questionnaire(7) at the relevant assessment as this will be considered physical activity outside of the trial.

8. Progressive resistance training procedure

- *Before commencing the intervention, determine the 6RM - 15RM as the heaviest weight that could be lifted through the participant's full range with good form*(8) *for 6-15 reps.*
- Identify muscle weakness and address through progressive resistance training procedure (Table 3).
- Focus on maintaining correct movement patterns and eccentric control (this take precedence over following the progressive resistance training procedure).
- Physiotherapist-facilitated movement can be utilised if participants have insufficient muscle strength to perform anti-gravity activity (and progressive resistance principles do not have to be followed).
- Facilitate postural control and/or alignment to isolate control for strengthening.
- Exercise multi-joint or larger muscle groups first.
- Eccentric control and multi-joint muscle exercises require a greater demand than concentric strengthening exercises(9, 10). Consider this when planning timing of strengthening exercises within program.
- If you include ballistic exercises, work to fatigue as appropriate.
- Aim to select key muscles to strengthen throughout the whole of the 30-week program as it may take 10 weeks to see benefits(11).
- If key areas change, you can modify strengthening program midway through the rehabilitation intervention to ensure 10-week strength training per muscle group chosen.
- For the HEP, avoid strengthening same muscle groups on consecutive days (aim three times per week for each muscle group selected).

Table 3. Strengthening protocol (*adapted from Kjølhede et al. 2015(12)*)

	Week	Sets	Reps	Intensity	Rest*
Outpatient Program	1–2	3	10	15 RM	2 minutes
	3–4	3	12	15 RM	2 minutes

	5–6	3	10	12 RM	2 minutes
Home Exercise Program	7–8	4	10	10 RM	2-3 minutes
	9–10	4	8	8 RM	2-3 minutes
	11–12	4	6	6 RM	3 minutes
	13–14	3	10	12 RM	2 minutes
	15–16	4	10	10 RM	2-3 minutes
	17–18	4	10	10 RM	2-3 minutes
	19–20	4	8	8 RM	2-3 min
	21–22	4	6	6 RM	3 min
	23–24	5	6	6 RM	3 min
	25-26	*3*	*10*	*12 RM*	*2 min*
	27-28	*4*	*10*	*10 RM*	*2-3 min*
	29-30	*4*	*8*	*8 RM*	*2-3 min*[β]

*Rest between sets; [β]Kjølhede et al (2015) program only documented up to 24 weeks, therefore the week 25-30 protocol is based on the American College of Sports Medicine position stand(10, 12). RM = Repetition Maximum; Reps = Repetitions.

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