


# BMJ Open 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

Sarah C Milne <sup>1,2,3,4</sup>, Louise A Corben,<sup>1,3,4</sup> Melissa Roberts,<sup>1,2</sup> David Szmulewicz,<sup>5,6,7,8</sup> J Burns,<sup>9</sup> Anneke C Grobler,<sup>4,10</sup> Shannon Williams,<sup>11,12</sup> Jillian Chua,<sup>13</sup> Christina Liang,<sup>14,15</sup> Phillipa J Lamont,<sup>16</sup> Alison C Grootendorst,<sup>17</sup> Libby Massey,<sup>17</sup> Carolyn Sue,<sup>14,15</sup> Kim Dalziel,<sup>18</sup> Desiree LaGrappe,<sup>17</sup> Liz Willis,<sup>17</sup> Aleka Freijah,<sup>19</sup> Paul Gerken,<sup>19</sup> Martin B Delatycki<sup>1,4,20</sup>

**To cite:** Milne SC, Corben LA, Roberts M, *et al.* 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. *BMJ Open* 2020;**10**:e040230. doi:10.1136/bmjopen-2020-040230

► Prepublication history and additional material for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2020-040230>).

Received 08 May 2020

Revised 11 November 2020

Accepted 25 November 2020



© Author(s) (or their employer(s)) 2020. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

For numbered affiliations see end of article.

## Correspondence to

Professor Martin B Delatycki; [martin.delatycki@vcgs.org.au](mailto:martin.delatycki@vcgs.org.au)

## 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,

## 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.

presented at national and/or international conferences and disseminated to Australian ataxia support groups.

**Trial registration number** ACTRN12618000908235.

## INTRODUCTION

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

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.<sup>4</sup> The main clinical features of hereditary cerebellar ataxia are typically gait and limb ataxia, impaired balance, oculomotor incoordination and dysarthria.<sup>5 6</sup> Progressive gait ataxia often leads to reduced mobility and functional independence in daily activities, with a significant negative impact on quality of life.<sup>7 8</sup>

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.<sup>5</sup> This may include extrapyramidal, pyramidal, brainstem, spinocerebellar tract, dorsal column, basal ganglia, vestibular and peripheral nerve pathology.<sup>9 10</sup> 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.<sup>9</sup>

Presently no pharmacological treatment has been conclusively shown to slow or halt disease progression in the hereditary cerebellar ataxias,<sup>11</sup> although research into treatment has advanced considerably over the last two decades.<sup>12</sup> 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.<sup>13–16</sup> It is suggested that greater frequency of exercise and challenging balance produce better outcomes for individuals with hereditary cerebellar ataxia.<sup>14 17–19</sup> Inpatient and outpatient rehabilitation programmes typically offer more intensive rehabilitation than community or home-based options. However, due to rising health-care costs and the progressive nature of the hereditary cerebellar ataxias, low-cost home-based programmes are often prescribed by clinicians<sup>20</sup> and implementation of more intensive outpatient treatment in clinical practice remains limited.<sup>21</sup>

Recent systematic reviews have identified over 20 studies examining rehabilitation, physical therapy or exercise for individuals with ataxia.<sup>15 22 23</sup> 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.<sup>14 24–29</sup> The conclusions that can be drawn are limited by underpowered sample sizes,<sup>14 24 25 27</sup> an absence of between-group statistical analyses<sup>24 25</sup> and no long-term follow-up<sup>14 25 27–29</sup> in many of the studies. The rarity of the hereditary cerebellar ataxias in combination with the challenges related

to recruitment in rehabilitation trials<sup>30</sup> 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

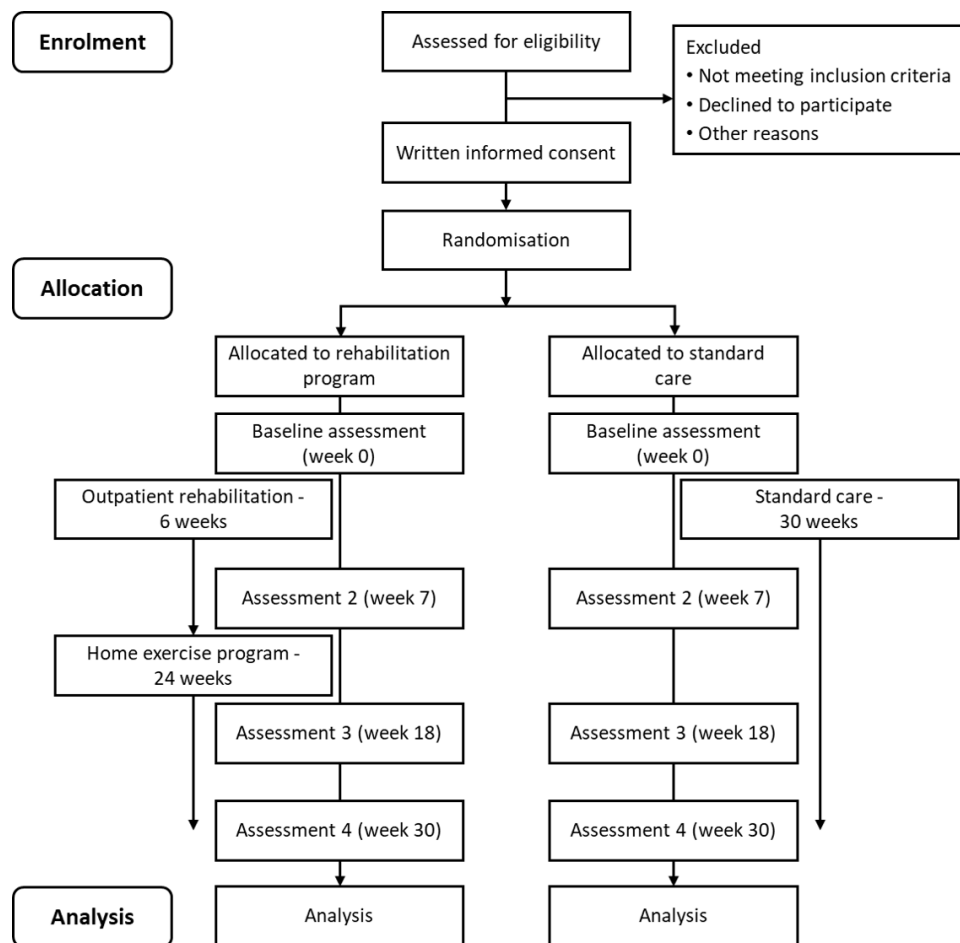
- ▶ To determine the effect of a 30-week individualised rehabilitation programme (6 weeks of intensive outpatient rehabilitation followed by 24 weeks of a supported home exercise programme) on motor function (measured by the motor domain of the Function Independence Measure (m-FIM)) as compared with 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<sup>31 32</sup> 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.<sup>14</sup> 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<sup>33</sup>) 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<sup>34</sup> and Parkinson disease<sup>35</sup> designed to maximise exercise completion.

The rehabilitation programme will be founded on six domains<sup>14</sup> 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

Domain	Key characteristics	Time spent per session (minutes)	
		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. <sup>54</sup> 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. <sup>19</sup> 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 <sup>17</sup> 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. <sup>55</sup> 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,<sup>20</sup> 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.<sup>36 37</sup> Scores will be attained by an FIM-certified assessor through structured interview with the participant<sup>38</sup> and observation during the assessment. Secondary outcome measures are: Scale for the Assessment and Rating of Ataxia<sup>39</sup>; Berg Balance Scale<sup>40</sup>; Patient Global Impression of Change (PGIC)<sup>41</sup>; Medical Outcomes Study 36 item Short-Form Health Survey V.2 (SF-36 v2)<sup>42</sup>; Function in Sitting Test<sup>43</sup>; postural control in sitting and standing with eyes open and eyes closed measured with the BioKin system<sup>44</sup> 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,<sup>45</sup> 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<sup>46</sup> and its potential influence on the effects (magnitude and ability to sustain improvement) of rehabilitation.<sup>17</sup> 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 15s.<sup>47</sup>

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<sup>48</sup>; falls history and quantity will be measured according to the Ashburn and colleagues<sup>49</sup> interview script and the European consensus definition<sup>50</sup> 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.<sup>14</sup> 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 <sup>37</sup>	<ul style="list-style-type: none"> <li>▶ The m-FIM evaluates a person's ability to perform motor activities of daily living.<sup>56</sup> Items include performance in self-care, sphincter control and mobility.<sup>57</sup></li> <li>▶ 13 items, each assessed against a 7-point ordinal scale.</li> <li>▶ Maximum score of 91 (complete independence) and a minimum of 13 (complete dependence).</li> </ul>	<ul style="list-style-type: none"> <li>▶ High validity and inter-rater reliability<sup>36 58</sup>.</li> <li>▶ More responsive to change after rehabilitation than the total FIM score for individuals with FRDA.<sup>14</sup></li> <li>▶ Exhibited strong correlations with level of disability in neurological populations and can predict amount of help required.<sup>36 59-61</sup></li> </ul>
Ataxia symptoms	SARA <sup>39</sup>	<ul style="list-style-type: none"> <li>▶ The SARA is a semiquantitative clinical assessment of ataxia, measuring ataxia of upper limb, lower limb, gait, balance and speech.</li> <li>▶ Eight items; score range 0–40, with a higher score indicating more severe ataxia.<sup>39</sup></li> </ul>	<ul style="list-style-type: none"> <li>▶ Excellent inter-rater and test–retest reliability in individuals with ataxia.<sup>39</sup></li> <li>▶ Excellent construct validity in ataxias of multiple aetiologies<sup>62 63</sup>.</li> </ul>
Balance	BBS <sup>40</sup>	<ul style="list-style-type: none"> <li>▶ The BBS evaluates performance in sitting and standing balance activities.</li> <li>▶ 14 items; score ranging 0–56 with a higher score indicating better balance.</li> </ul>	<ul style="list-style-type: none"> <li>▶ Responsive to change after intensive coordinative training in degenerative ataxias.<sup>17</sup></li> <li>▶ Good intra- and inter-rater reliability when assessing balance in people with ataxia secondary to multiple sclerosis.<sup>64</sup></li> </ul>
Participant perceived benefit	PGIC <sup>41</sup>	<ul style="list-style-type: none"> <li>▶ The PGIC is 7-point numerical rating scale measuring global benefit from the participant's perspective.</li> <li>▶ 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).</li> <li>▶ Cut-off for clinically meaningful change will be 5 (moderately better, and a slight but noticeable change).</li> </ul>	<ul style="list-style-type: none"> <li>▶ High face validity.<sup>65</sup></li> <li>▶ Responsive to change following a 6 week rehabilitation programme in individuals with FRDA.<sup>14</sup></li> <li>▶ Used as an external criterion for determining smallest detectable and clinically meaningful change after rehabilitation and 1 year of natural decline in individuals with multiple sclerosis and spinocerebellar ataxia respectively<sup>66 67</sup>.</li> </ul>
Quality of life	SF-36 v2 <sup>42</sup>	<ul style="list-style-type: none"> <li>▶ The SF-36 v2 measures self-perceived health-related quality of life.</li> <li>▶ 36 items; yields scores for eight multiitem dimensions and two summary scale scores (physical and mental health).<sup>42</sup></li> </ul>	<ul style="list-style-type: none"> <li>▶ Responsive to reduction in quality of life in individuals with ataxia<sup>68 69</sup>.</li> <li>▶ 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.<sup>68</sup></li> <li>▶ The Sf-36 v1 has shown acceptable internal consistency among subscales in individuals with FRDA.<sup>70</sup></li> </ul>
Daily walking activity	<ol style="list-style-type: none"> <li>1. Average daily step count.</li> <li>2. Average daily distance walked.</li> </ol>	<ul style="list-style-type: none"> <li>▶ Measured with the Fitbit Flex 2, a commercial grade tri-axial accelerometer worn on the wrist.</li> <li>▶ Worn for 24 hours per day for seven consecutive days.</li> <li>▶ A valid day=Fitbit Flex 2 worn for ≥90% of the day. Wear time will be recorded by participant self-report.</li> </ul>	<ul style="list-style-type: none"> <li>▶ 3–5 days of accelerometer monitoring in adults is necessary to achieve a between day intra-class correlation of 0.80.<sup>71</sup></li> <li>▶ Moderate validity for measuring physical activity relative to the Actigraph.<sup>72</sup> Good to excellent significant positive correlations and agreement with the Actigraph, although it overestimates number of steps.<sup>73</sup></li> <li>▶ Excellent reliability in an older population.<sup>74</sup></li> </ul>

Continued



Table 2 Continued

Outcome	Measure	Description	Psychometric properties
Sitting balance	FIST <sup>43</sup>	<ul style="list-style-type: none"> <li>▶ The FIST is a clinical measure of sitting balance.<sup>43</sup></li> <li>▶ 14 items; score ranging 0–56 with a higher score indicating better sitting balance.<sup>43</sup></li> </ul>	<ul style="list-style-type: none"> <li>▶ Excellent concurrent validity with the BBS and moderate to good validity with the m-FIM in adults with neurological deficits and impaired sitting balance.<sup>75</sup></li> <li>▶ Excellent test–retest reliability in individuals with various neurological disorders<sup>76 77</sup>.</li> <li>▶ Responsive to change following rehabilitation and a minimal detectable change of 5.5 points.<sup>75</sup></li> </ul>
Postural control	3D movement of the trunk in sitting and standing with eyes open and closed.	<ul style="list-style-type: none"> <li>▶ Measured with the BioKin system, a wireless motion capture device.<sup>44</sup></li> <li>▶ Four test conditions include: sitting 30s, no foot contact on the floor, arms out straight: (1) eyes open and (2) eyes closed; standing 30s, feet together: (3) eyes open and (4) eyes closed.</li> </ul>	<ul style="list-style-type: none"> <li>▶ An exploratory outcome used in this trial, not previously validated in this population.</li> </ul>

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<sup>14</sup> 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<sup>51</sup> 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).

### 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.<sup>52</sup> 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

### 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.



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.<sup>14</sup> 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 forms (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.<sup>53</sup> 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.

### Author affiliations

<sup>1</sup>Bruce Lefroy Centre for Genetic Health Research, Murdoch Children’s Research Institute, Parkville, Victoria, Australia

<sup>2</sup>Physiotherapy Department, Monash Health, Cheltenham, Victoria, Australia

<sup>3</sup>School of Primary and Allied Health Care, Monash University, Frankston, Victoria, Australia

- <sup>4</sup>Department of Paediatrics, The University of Melbourne, Parkville, Victoria, Australia  
<sup>5</sup>Balance Disorders & Ataxia Service, Royal Victorian Eye and Ear Hospital, East Melbourne, Victoria, Australia  
<sup>6</sup>Cerebellar Ataxia Clinic, Alfred Health, Caulfield, Victoria, Australia  
<sup>7</sup>Monash Medical Centre, Monash Health, Clayton, Victoria, Australia  
<sup>8</sup>The Florey Institute of Neuroscience and Mental Health, Parkville, Victoria, Australia  
<sup>9</sup>University of Sydney School of Health Sciences, Faculty of Medicine and Health & Children's Hospital at Westmead, Sydney, New South Wales, Australia  
<sup>10</sup>Clinical Epidemiology and Biostatistics Unit, Murdoch Children's Research Institute, Parkville, Victoria, Australia  
<sup>11</sup>Physiotherapy Department, Royal Perth Hospital, Perth, Western Australia, Australia  
<sup>12</sup>Physiotherapy Department, Sir Charles Gairdner Hospital, Nedlands, Western Australia, Australia  
<sup>13</sup>Physiotherapy Department, Ryde Hospital, Eastwood, New South Wales, Australia  
<sup>14</sup>Department of Neurology, Royal North Shore Hospital, St Leonards, New South Wales, Australia  
<sup>15</sup>Kolling Institute of Medical Research, University of Sydney, St Leonards, New South Wales, Australia  
<sup>16</sup>Neurogenetic Unit, Royal Perth Hospital, Perth, Western Australia, Australia  
<sup>17</sup>MJD Foundation, Darwin, Northern Territory, Australia  
<sup>18</sup>Melbourne School of Population and Global Health, University of Melbourne, Parkville, Victoria, Australia  
<sup>19</sup>Rehabilitation Services, Royal Darwin and Palmerston Hospitals, Darwin, Northern Territory, Australia  
<sup>20</sup>Victorian Clinical Genetics Services, Melbourne, Victoria, Australia

**Acknowledgements** The authors would like to thank all the participants who give their time for this study. The authors would also like to thank the Physiotherapy Departments at the Kingston Centre, Ryde Hospital, Sir Charles Gairdner Hospital and Royal Darwin Hospital for their support. Thank you to the Cerebellar Ataxia Australia Association and the Friedreich Ataxia Network for their assistance in recruiting for this study. Thank you to the Anindilyakwa Land Council which gave support and granted permission to conduct this research on their lands.

**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, P.JL, 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.

**Funding** This work was supported by an Australian Government Medical Research Future Fund (MRFF) Lifting Clinical Trials and Registries Capacity Program Grant, number (APP1152226) and a Rebecca L Cooper grant, number (PG2018135). LC is funded by a MRFF Career Development Fellowship, number (APP1143098). The funders are not involved in the study design, the collection, analysis and interpretation of data, nor the writing of the manuscript.

**Competing interests** None declared.

**Patient consent for publication** Not required.

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Supplemental material** This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

**Open access** This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>.

## ORCID iD

Sarah C Milne <http://orcid.org/0000-0002-9406-8609>

## REFERENCES

- 1 Sarva H, Shanker VL. Treatment options in degenerative cerebellar ataxia: a systematic review. *Mov Disord Clin Pract* 2014;1:291–8.
- 2 Bird TD. Hereditary ataxia overview. In: Adam MP, Ardinger HH, Pagan RA, et al, eds. *GeneReviews® [Internet]*. Seattle (WA): University of Washington, Seattle, 1993–2020. <https://www.ncbi.nlm.nih.gov/books/NBK1138/>
- 3 Pilotto F, Saxena S. Epidemiology of inherited cerebellar ataxias and challenges in clinical research. *Clinical and Translational Neuroscience* 2018;2:2514183X1878525.
- 4 Ruano L, Melo C, Silva MC, et al. The global epidemiology of hereditary ataxia and spastic paraplegia: a systematic review of prevalence studies. *Neuroepidemiology* 2014;42:174–83.
- 5 Paulson HL. The spinocerebellar ataxias. *J Neuroophthalmol* 2009;29:227–37.
- 6 Bidichandani SI, Delatycki MB. Friedreich ataxia. In: Adam MP, Ardinger HH, Pagan RA, et al, eds. *GeneReviews™ [Internet]*. Seattle (WA): University of Washington, Seattle, 1993–2020. [www.ncbi.nlm.nih.gov/books/NBK1281/](http://www.ncbi.nlm.nih.gov/books/NBK1281/)
- 7 Wilson CL, Fahey MC, Corben LA, et al. Quality of life in Friedreich ataxia: what clinical, social and demographic factors are important? *Eur J Neurol* 2007;14:1040–7.
- 8 White VB, Leib JR, Farmer JM, et al. Exploration of transitional life events in individuals with Friedreich ataxia: implications for genetic counseling. *Behav Brain Funct* 2010;6:65.
- 9 Klockgether T, Mariotti C, Paulson HL. Spinocerebellar ataxia. *Nat Rev Dis Primers* 2019;5:24.
- 10 Koeppen AH, Mazurkiewicz JE. Friedreich ataxia: neuropathology revised. *J Neuropathol Exp Neurol* 2013;72:78–90.
- 11 Bürk K. Friedreich ataxia: current status and future prospects. *Cerebellum Ataxias* 2017;4:4.
- 12 Tai G, Corben LA, Yiu EM, et al. Progress in the treatment of Friedreich ataxia. *Neurol Neurochir Pol* 2018;52:129–39.
- 13 Cassidy E, Naylor S, Reynolds F. The meanings of physiotherapy and exercise for people living with progressive cerebellar ataxia: an interpretative phenomenological analysis. *Disabil Rehabil* 2018;40:894–904.
- 14 Milne SC, Corben LA, Roberts M, et al. Can rehabilitation improve the health and well-being in Friedreich's ataxia: a randomized controlled trial? *Clin Rehabil* 2018;32:630–43.
- 15 Synofzik M, Ilg W. Motor training in degenerative spinocerebellar disease: ataxia-specific improvements by intensive physiotherapy and exergames. *Biomed Res Int* 2014;2014:1–11.
- 16 de Silva RN, Vallortigara J, Greenfield J, et al. Diagnosis and management of progressive ataxia in adults. *Pract Neurol* 2019;19:196–207.
- 17 Ilg W, Synofzik M, Brötzel D, et al. Intensive coordinative training improves motor performance in degenerative cerebellar disease. *Neurology* 2009;73:1823–30.
- 18 Ilg W, Schatton C, Schicks J, et al. Video game-based coordinative training improves ataxia in children with degenerative ataxia. *Neurology* 2012;79:2056–60.
- 19 Keller JL, Bastian AJ. A home balance exercise program improves walking in people with cerebellar ataxia. *Neurorehabil Neural Repair* 2014;28:770–8.
- 20 Cassidy E, Reynolds F, Naylor S, et al. Using interpretative phenomenological analysis to inform physiotherapy practice: an introduction with reference to the lived experience of cerebellar ataxia. *Physiother Theory Pract* 2011;27:263–77.
- 21 Maring J, Croarkin E, Morgan S, et al. Perceived effectiveness and barriers to physical therapy services for families and children with Friedreich ataxia. *Pediatr Phys Ther* 2013;25:305–13.
- 22 Milne SC, Corben LA, Georgiou-Karistianis N, et al. Rehabilitation for individuals with genetic degenerative ataxia: a systematic review. *Neurorehabil Neural Repair* 2017;31:609–22.
- 23 Fonteyn EMR, Keus SHJ, Verstappen CCP, et al. The effectiveness of allied health care in patients with ataxia: a systematic review. *J Neurol* 2014;261:251–8.
- 24 Seco CJ, Fernandez IG, Verdejol IC, et al. Improvements in quality of life in individuals with Friedreich's ataxia after participation in a 5-year program of physical activity: an observational study pre-post test design, and two years follow-up. *Int J Neurorehabil* 2014;1:129.
- 25 Chang Y-J, Chou C-C, Huang W-T, et al. Cycling regimen induces spinal circuitry plasticity and improves leg muscle coordination in individuals with spinocerebellar ataxia. *Arch Phys Med Rehabil* 2015;96:1006–13.

- 26 Miyai I, Ito M, Hattori N, *et al.* Cerebellar ataxia rehabilitation trial in degenerative cerebellar diseases. *Neurorehabil Neural Repair* 2012;26:515–22.
- 27 Bunn LM, Marsden JF, Giunti P, *et al.* Training balance with optokinetic stimuli in the home: a randomized controlled feasibility study in people with pure cerebellar disease. *Clin Rehabil* 2015;29:143–53.
- 28 Velázquez-Pérez L, Rodríguez-Díaz JC, Rodríguez-Labrada R, *et al.* Neurorehabilitation improves the motor features in prodromal SCA2: a randomized, controlled trial. *Mov Disord* 2019;34:1060–8.
- 29 Rodríguez-Díaz JC, Velázquez-Pérez L, Rodríguez Labrada R, *et al.* Neurorehabilitation therapy in spinocerebellar ataxia type 2: a 24-week, rater-blinded, randomized, controlled trial. *Mov Disord* 2018;33:1481–7.
- 30 Blanton S, Morris DM, Prettyman MG, *et al.* Lessons learned in participant recruitment and retention: the excite trial. *Phys Ther* 2006;86:1520–33.
- 31 Harris PA, Taylor R, Minor BL, *et al.* The REDCap Consortium: building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
- 32 Harris PA, Taylor R, Thielke R, *et al.* Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform* 2009;42:377–81.
- 33 Turner-Stokes L, Williams H. Goal attainment scaling: a direct comparison of alternative rating methods. *Clin Rehabil* 2010;24:66–73.
- 34 Burns J, Sman AD, Cornett KMD, *et al.* Safety and efficacy of progressive resistance exercise for Charcot-Marie-Tooth disease in children: a randomised, double-blind, sham-controlled trial. *Lancet Child Adolesc Health* 2017;1:106–13.
- 35 van der Kolk NM, de Vries NM, Penko AL, *et al.* A remotely supervised home-based aerobic exercise programme is feasible for patients with Parkinson's disease: results of a small randomised feasibility trial. *J Neurol Neurosurg Psychiatry* 2018;89:1003–5.
- 36 Hall KM, Hamilton BB, Gordon WA, *et al.* Characteristics and comparisons of functional assessment indices: disability rating scale, functional independence measure, and functional assessment measure. *J Head Trauma Rehabil* 1993;8:60–74.
- 37 Hsueh I-P, Lin J-H, Jeng J-S, *et al.* Comparison of the psychometric characteristics of the functional independence measure, 5 item Barthel index, and 10 item Barthel index in patients with stroke. *J Neurol Neurosurg Psychiatry* 2002;73:188–90.
- 38 Young Y, Fan M-Y, Hebel JR, *et al.* Concurrent validity of administering the functional independence measure (FIM) instrument by interview. *Am J Phys Med Rehabil* 2009;88:766–70.
- 39 Schmitz-Hübisch T, du Montcel ST, Baliko L, *et al.* Scale for the assessment and rating of ataxia: development of a new clinical scale. *Neurology* 2006;66:1717–20.
- 40 Berg KE *et al.* Measuring balance in the elderly: preliminary development of an instrument. *Physiotherapy Canada* 1989;41:304–11.
- 41 Hurst H, Bolton J. Assessing the clinical significance of change scores recorded on subjective outcome measures. *J Manipulative Physiol Ther* 2004;27:26–35.
- 42 Jenkinson C, Stewart-Brown S, Petersen S, *et al.* Assessment of the SF-36 version 2 in the United Kingdom. *J Epidemiol Community Health* 1999;53:46–50.
- 43 Gorman SL, Radtka S, Melnick ME, *et al.* Development and validation of the function in sitting test in adults with acute stroke. *J Neurol Phys Ther* 2010;34:150–60.
- 44 Ekanayake SW, Morris AJ, Forrester M, *et al.* BioKin: an ambulatory platform for gait kinematic and feature assessment. *Healthc Technol Lett* 2015;2:40–5.
- 45 Gill DP, Jones GR, Zou GY, *et al.* The phone-FITT: a brief physical activity interview for older adults. *J Aging Phys Act* 2008;16:292–315.
- 46 Kremmyda O, Kirchner H, Glasauer S, *et al.* False-positive head-impulse test in cerebellar ataxia. *Front Neurol* 2012;3:162.
- 47 Subramony SH, May W, Lynch D, *et al.* Measuring Friedreich ataxia: interrater reliability of a neurologic rating scale. *Neurology* 2005;64:1261–2.
- 48 Brusse E, Brusse-Keizer MGJ, Duivenvoorden HJ, *et al.* Fatigue in spinocerebellar ataxia: patient self-assessment of an early and disabling symptom. *Neurology* 2011;76:953–9.
- 49 Ashburn A, Stack E, Ballinger C, *et al.* The circumstances of falls among people with Parkinson's disease and the use of falls diaries to facilitate reporting. *Disabil Rehabil* 2008;30:1205–12.
- 50 Kellogg IWG. The prevention of falls in later life. A report of the Kellogg international work group on the prevention of falls by the elderly. *Dan Med Bull* 1987;34:1–24.
- 51 Khan F, Pallant JF, Brand C, *et al.* Effectiveness of rehabilitation intervention in persons with multiple sclerosis: a randomised controlled trial. *J Neurol Neurosurg Psychiatry* 2008;79:1230–5.
- 52 Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002;21:271–92.
- 53 Lin JY, Lu Y. Establishing a data monitoring Committee for clinical trials. *Shanghai Arch Psychiatry* 2014;26:54–6.
- 54 Kjølhede T, Vissing K, de Place L, *et al.* Neuromuscular adaptations to long-term progressive resistance training translates to improved functional capacity for people with multiple sclerosis and is maintained at follow-up. *Mult Scler* 2015;21:599–611.
- 55 Aman JE, Elangovan N, Yeh I-L, *et al.* The effectiveness of proprioceptive training for improving motor function: a systematic review. *Front Hum Neurosci* 2014;8:1075.
- 56 Fahey MC, Corben L, Collins V, *et al.* How is disease progress in Friedreich's ataxia best measured? A study of four rating scales. *J Neurol Neurosurg Psychiatry* 2007;78:411–3.
- 57 Smith PM, Illig SB, Fiedler RC, *et al.* Intermodal agreement of follow-up telephone functional assessment using the functional independence measure in patients with stroke. *Arch Phys Med Rehabil* 1996;77:431–5.
- 58 Delatycki MB. Evaluating the progression of Friedreich ataxia and its treatment. *J Neurol* 2009;256 Suppl 1:36–41.
- 59 Granger CV, Cotter AC, Hamilton BB, *et al.* Functional assessment scales: a study of persons after stroke. *Arch Phys Med Rehabil* 1993;74:133–8.
- 60 Granger CV, Cotter AC, Hamilton BB, *et al.* Functional assessment scales: a study of persons with multiple sclerosis. *Arch Phys Med Rehabil* 1990;71:870–5.
- 61 Hobart JC, Lamping DL, Freeman JA, *et al.* Evidence-Based measurement: which disability scale for neurologic rehabilitation? *Neurology* 2001;57:639–44.
- 62 Saute JAM, Donis KC, Serrano-Munuera C, *et al.* Ataxia rating scales—psychometric profiles, natural history and their application in clinical trials. *Cerebellum* 2012;11:488–504.
- 63 Bürk K, Mälzig U, Wolf S, *et al.* Comparison of three clinical rating scales in Friedreich ataxia (FRDA). *Mov Disord* 2009;24:1779–84.
- 64 Winsor S, Smith CM, Hale LA, *et al.* Psychometric properties of a core set of measures of balance for people with cerebellar ataxia secondary to multiple sclerosis. *Arch Phys Med Rehabil* 2017;98:270–6.
- 65 Fischer Det *et al.* Capturing the Patient's View of Change as a Clinical Outcome Measure. *J Am Med Assoc* 1999;282:1157–62.
- 66 Baert I, Freeman J, Smedal T, *et al.* Responsiveness and clinically meaningful improvement, according to disability level, of five walking measures after rehabilitation in multiple sclerosis: a European multicenter study. *Neurorehabil Neural Repair* 2014;28:621–31.
- 67 Schmitz-Hübisch T, Fimmers R, Rakowicz M, *et al.* Responsiveness of different rating instruments in spinocerebellar ataxia patients. *Neurology* 2010;74:678–84.
- 68 Tai G, Corben LA, Yiu EM, *et al.* A longitudinal study of the SF-36 version 2 in Friedreich ataxia. *Acta Neurol Scand* 2017;136:41–6.
- 69 Sánchez-López CR, Perestelo-Pérez L, Escobar A, *et al.* Health-Related quality of life in patients with spinocerebellar ataxia. *Neurologia* 2017;32:143–51.
- 70 Epstein E, Farmer JM, Tsou A, *et al.* Health related quality of life measures in Friedreich ataxia. *J Neurol Sci* 2008;272:123–8.
- 71 Matthews CE, Ainsworth BE, Thompson RW, *et al.* Sources of variance in daily physical activity levels as measured by an accelerometer. *Med Sci Sports Exerc* 2002;34:1376–81.
- 72 Sushames A, Edwards A, Thompson F, *et al.* Validity and reliability of Fitbit flex for step count, moderate to vigorous physical activity and activity energy expenditure. *PLoS One* 2016;11:e0161224.
- 73 Chu AHY, Ng SHX, Paknezhad M, *et al.* Comparison of wrist-worn Fitbit flex and waist-worn ActiGraph for measuring steps in free-living adults. *PLoS One* 2017;12:e0172535.
- 74 Burton E, Hill KD, Lautenschlager NT, *et al.* Reliability and validity of two fitness tracker devices in the laboratory and home environment for older community-dwelling people. *BMC Geriatr* 2018;18:103.
- 75 Gorman SL, Harro CC, Platko C, *et al.* Examining the function in sitting test for validity, responsiveness, and minimal clinically important difference in inpatient rehabilitation. *Arch Phys Med Rehabil* 2014;95:2304–11.
- 76 Sung J, Ousley CM, Shen S, *et al.* Reliability and validity of the function in sitting test in nonambulatory individuals with multiple sclerosis. *Int J Rehabil Res* 2016;39:308–12.
- 77 Abou L, Sung J, Sosnoff JJ, *et al.* Reliability and validity of the function in sitting test among non-ambulatory individuals with spinal cord injury. *J Spinal Cord Med* 2019:1–8.