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Physical activity and exercise outcomes in Huntington's disease (PACE-HD): results of a 12-month trial-within-cohort feasibility study of a physical activity intervention in people with Huntington's disease

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ABSTRACT

Introduction: While physical activity (PA) is recognized as important in Huntington's disease (HD) disease management, there has been no long-term evaluation undertaken. We aimed to evaluate the feasibility of a nested (within cohort) randomized controlled trial (RCT) of a physical therapist-led PA intervention.
Methods: Participants were recruited from six HD specialist centers participating in the Enroll-HD cohort study in Germany, Spain and U.S. Assessments were completed at baseline and 12 months and linked to Enroll-HD cohort data. Participants at three sites (cohort) received no contact between baseline and 12 month assessments. Participants at three additional sites (RCT) were randomized to PA intervention or control group. The intervention consisted of 18 sessions delivered over 12 months; control group participants received no intervention, however both groups completed monthly exercise/falls diaries and 6-month assessments.
Results: 274 participants were screened, 204 met inclusion criteria and 116 were enrolled (59 in cohort; 57 in RCT). Retention rates at 12-months were 84.7% (cohort) and 79.0% (RCT). Data completeness at baseline ranged from 42.3 to 100% and at 12-months 19.2–85.2%. In the RCT, there was 80.5% adherence, high intervention fidelity, and similar adverse events between groups. There were differences in fitness, walking endurance and self-reported PA at 12 months favoring the intervention group, with data completeness >60%. Participants in the cohort had motor and functional decline at rates comparable to previous studies.
Conclusion: Predefined progression criteria indicating feasibility were met. PACE-HD lays the groundwork for a future, fully-powered within cohort trial, but approaches to ensure data completeness must be considered.
Clinicaltrials.gov: NCT03344601.

1. Introduction

Evaluation of exercise and physical activity (PA) interventions for people with Huntington's disease (HD), as both stand-alone or adjunctive therapy, has never been more relevant, even as the search for disease-modifying therapies continues. Although several exciting

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options for disease modification are emerging [1], translating these into clinical practice is difficult and time lines for achieving translation are uncertain [2]. PA interventions may be required to optimise the impact of other therapies, such as cell replacement therapies, where training plays a key role in promoting integration and function of the graft [3]. These interventions have an important role in addressing the complex disease symptoms in HD, including motor, cognitive and behavioral impairments, which result in loss of independence and impact quality of life [4].

Short-term (6–8 weeks) intervention studies provide preliminary support for the benefits of PA in HD in terms of motor function as well as patient-reported physical and social benefits [5]. Results from longer term, multi-disciplinary interventions have demonstrated stabilization or improvement in functional outcomes and changes in brain structure [6–9]. However, it is difficult to identify which components of these multi-faceted interventions, which can include physical, occupational and speech therapy as well as cognitive and social interventions, are driving outcomes [10].

While there has been a move towards models of primary and secondary prevention across many countries, prompted by the World Health Organization (WHO) [11], implementation in practice is limited. Rehabilitation interventions for people with HD typically involve tertiary prevention, where therapists work to remediate activity limitations following the onset of motor impairments secondary to disease progression [12]. Intervening at this stage is incongruent with existing literature on neurodegenerative diseases, which suggests that PA plays a crucial role in preventing and delaying neurodegeneration by specifically targeting neuroprotective mechanisms [13]. Furthermore, as HD is a slowly progressing disease, interventions delivered over short periods are likely not optimal for long-term management [12]. A new model of care with ongoing consultation starting in earlier disease stages, including presymptomatically, may be needed to facilitate PA for effective management of neurodegenerative diseases [14].

HD is a rare neurodegenerative disease, presenting many logistical challenges in implementing large scale studies of PA alongside competitive recruitment of ongoing trials. Pragmatic study designs, such as trial within cohort (TWiC) have the potential to improve trial efficiency and generalizability of results [15,16], with added potential for conducting multiple evaluations within the same cohort. As a step towards applying scientific rigor to the study of PA in HD, we aimed to establish the feasibility of a TWiC of a 12-month PA intervention in people with HD. Enroll-HD, a longitudinal cohort study with over 20,000 participants in 22 countries, provided the platform for the nested RCT that also enabled us to evaluate progression in a cohort of individuals with HD compared to those in the RCT [17]. This was particularly relevant given the knowledge that participants may alter their behavior simply due to participating in a clinical trial [18].

The primary objective of this study was to evaluate feasibility of a TWiC of a physical-therapy led intervention in terms of recruitment, retention, data completeness, adherence, fidelity and acceptability. Secondary objectives were to explore (1) effect estimates for long-term PA in HD; (2) the influence of PA and fitness on cognitive, motor and functional abilities over a one-year period; and (3) the predictive validity of physical fitness at 6-months on motor and cognitive outcomes.

2. Methods

2.1. Study population

Participants were recruited at six Enroll-HD (https://enroll-hd.org/) sites. Three sites (Columbia University HDSA Center of Excellence and Teachers College, Columbia University, New York, NY; George Huntington Institute, Munster, Germany; and Hospital Universitario Fundacio Jimenez Diaz, Madrid, Spain) served as observational sites only (cohort). Three additional sites (University of California Los Angeles and re + active Physical Therapy, Los Angeles, CA, US; Ulm Medical Center, Ulm, Germany and University Hospital Aachen, Aachen, Germany; and Hospital Mare de Deu de la Merce, Barcelona, Spain) conducted the nested RCT. Eligible participants were identified from local Enroll-HD records. Inclusion criteria were: 1) confirmed genetic diagnosis of HD, 2) over 18 years of age, 3) currently registered as a participant in Enroll-HD, and 4) manifest HD, up to and including Shoulson-Fahn stage 2 disease status (defined as having a Total Functional Capacity of 7–13, indicating early-mid disease stage) [19]. Exclusion criteria were: 1) diagnosis of juvenile onset HD, 2) history of co-morbid neurological conditions such as multiple sclerosis or stroke, 3) an acute orthopedic condition, e.g. a sprained ankle or fracture, and 4) inability or unwillingness to give written informed consent.

2.2. Sample size

As a feasibility study, hypothesis testing was not indicated; a formal sample size calculation for efficacy was not performed. For a total sample size of 120 participants recruited into the study we were able to determine a 95% confidence interval (CI) for a 70% retention rate to within ±8.2%.

2.3. Assessments

Demographic and disease-specific measures were obtained through linkage with the Enroll-HD dataset.[1] Core and extended battery datasets are collected annually[2] from research participants as part of this multicenter longitudinal observational study [17]. We obtained the following data: age; sex; pharmacotherapy; CAG repeat length; Unified Huntington Disease Rating Scale (UHDRS), which includes Total Functional Capacity (TFC), Total Motor Score (TMS), Functional Assessment (FA), and Independence Scale (IS) [20]; Symbol Digital Modality Test (SDMT) [21]; Short Problem Behavior Assessment (PBA-s) [22]; Hospital Anxiety and Depression Scale combined with the Snaith Irritability Scale (HADS-SIS) [23,24]; SF-12 [25]; Timed Up and Go (TUG) [26] and 30-s chair stand test (30sCST) [27].

Concomitant pharmacotherapies were coded using the World Health Organization Drug Dictionary (WHO-DD). Indications for each drug were coded using the Medical Dictionary for Regulatory Activities.[3]

Participants completed a prospective PA and functional assessment battery (PACE-HD assessment battery) at baseline and 12 months, conducted within ± 6 weeks of annual Enroll-HD visit. Visit windows for 12-month Enroll-HD assessments were ± 3 months. Participants were screened using the Physical Activity Readiness Questionniare (PAR-Q) [28], and if needed were referred to their doctor for medical clearance. PACE-HD assessments included aerobic fitness (predicted VO_{2max}) [29,30], walking endurance (6 min walk) [31,32], HD-specific symptoms (HD-PRO-TRIAD) [33], self-reported PA (International Physical Activity Questionnaire-short form, IPAQ) [32,34] and Brunel Lifestyle Questionnaire [35]), accelerometer-based PA and step counts [36] using wrist-worn Geneactiv devices (Activinsights, Cambridgeshire, UK), Clinch Token Transfer Test [37] and Q-motor [38]. Participants in the RCT completed an additional 6-month interim assessment to assess the feasibility of collecting interim data for mediation analyses.

2.4. Randomization and blinding

For the RCT, 53 participants were randomly assigned 1:1 to either intervention or control group. Randomization was performed using a minimization technique via the study database to maintain allocation

[1] Enroll-HD; *https://Enroll-HD.org*.

[2] Enroll-HD data are routinely monitored for quality and accuracy and all data is subject to a quality control process prior to release.

[3] MedDRA; *https://www.meddra.org/*.

concealment. Randomization allowed for balancing by age (< or >50 years),[4] gender and motor impairment (UHDRS-TMS < or >40) and was stratified by country. For pragmatic reasons neither participants nor assessors were blinded to allocation.

2.5. Intervention

PACE-HD is based on knowledge developed in two previous studies: Exert-HD [39], an aerobic and strengthening exercise intervention, and Engage-HD [40], a physical activity coaching intervention. The PACE-HD intervention, which is described in detail in our protocol paper [41], was delivered in up to 18 sessions over 12 months by trained, licensed physical therapists and incorporated physical activity coaching and focused on promoting strategies for participants to engage in PA and specifically aerobic exercise. The intervention used a disease-specific workbook,[5] translated into Spanish and German, and participant-coach interactions grounded in self-determination theory (SDT) [42], which incorporates collaborative regulation that considers social–contextual-disease specific conditions [43]. The timing and location (at participant's home or at clinical sites) of these sessions was determined collaboratively between participant and therapist. If in-person visits were not possible due to travel-related issues, including restrictions due to COVID-19, therapists conducted sessions via video-conferencing or phone call. In partnership with the therapist, participants developed activity goals that were monitored and adjusted throughout the intervention. Therapists used activity goals to tailor exercise programs, with an aim of building up to 30-min periods of moderate-vigorous exercise 3–5 times per week, which could include aerobic and strength-based activities. Target heart rate (HR) for exercise was 65–85% of HR max, which was determined based on cycle ergometer testing at baseline. Participants were given wearable activity monitors (Fitbit Charge 2) to monitor PA, and therapists reviewed activity levels (e.g. step counts, activity intensity and frequency) using the Fitabase web-based program.[6] Participants in the control group were asked to continue with usual level of PA over 12 months. Participants in both groups were asked to keep monthly diaries, which were facilitated by phone calls by site coordinators or therapists to record the amount and type of PA as well as falls. The cohort group received no interaction beyond baseline and follow up assessments.

2.6. Training

Physical therapists (between 2 and 4 per intervention site) participated in one day training, which involved discussion of SDT theory underpinning the intervention framework. A therapist manual (available upon request) provided further guidance on the structured approach to sessions, focusing on exercise uptake and engagement in regular PA. Ongoing support and feedback phone calls to therapists were provided.

2.7. Data collection, management and linkage

PACE-HD data were entered into a custom-built database accessed via a secure web interface, after which it was automatically stored in a structured query language (SQL) database. The database was engineered with in-built validations and rigorously tested to ensure data quality. We used a back-end service platform, Fitabase (Small Steps Labs, LLC, San Diego, CA), to aggregate participant Fitbit data (intervention group only).

Demographic and disease specific data were obtained from Enroll-HD via a Specified Data Request.[7] Data were monitored remotely for completeness and validity throughout recruitment and follow-up via the study database.

2.8. Data analysis

Descriptive statistics were used to summarize demographic characteristics and outcome assessments. Pharmacotherapy was reported by indication, namely drugs prescribed for HD associated symptoms including (a) movement disorder (chorea, rigidity, bradykinesia); (b) anxiety, depression and apathy; (c) psychoses (d) irritability and (e) sleep disorder [44]. Given the known impact of beta-blocking agents on exercise response [45], we also included a beta-blocker category.

The primary feasibility outcome was the proportion of randomized participants that were followed-up at 12 months (retention), which was summarized alongside 95% CIs. For the RCT, adherence was measured as % of sessions attended out of 18 for the intervention group. Safety was assessed by calculating the number of adverse events as well as number of falls in intervention and control groups. Intervention fidelity was measured using a combination of therapist self-report checklists completed after each session (indicating whether sessions were consistent with protocol and training manual) and therapist self-assessment rating scale [46]. The rating scale was administered three times across intervention delivery (recommended after sessions 2, 6 and 15), and included three subscales related to SDT (autonomy, competence, relatedness) and general impression. Scores ranged from 0 to 4, which were averaged (higher scores indicated greater fidelity). As an additional measure of fidelity, we summarized Fitbit data including average number of days participants had Fitbit devices and percentage of days with valid wear time (defined as ≥10 h). Participant acceptability of the intervention was assessed from summary data tabulated from a purpose-developed Likert-scale questionnaire. Questions were underpinned by SDT and collaborative regulation mapping to the PACE-HD intervention logic model and inquired about satisfaction, enjoyment, participation, and ability to participate in the intervention over time.

Secondary efficacy outcomes from the RCT groups were presented with adjusted mean differences and 95% CIs. Analysis was intention-to-treat and complete case (we do not report effect estimates where data completion was less than 60% at baseline and 12 months). Linear models were used for continuous outcomes where the distributional assumptions were met and logistic regression for dichotomous outcomes with results presented as odds ratios and 95% CIs. Covariates in the models included individual participant characteristics used to balance the randomization (age, gender, TMS) and the baseline score for each respective outcome. Predicted VO_{2max} was adjusted only for TMS since it is already age and gender adjusted. We also calculated Cohen's d to provide an indication of within group change over a 12 month period for the three groups.

The feasibility of collecting interim data for mediation analysis was also assessed. Exploratory analysis was carried out using structural equation models of UHDRS TMS and HD-PRO-TRIAD mediated via physical fitness (total Watts from predicted Vo_{2max} test) at 6 months to assess the role of PA and fitness on cognitive, motor and functional abilities both individually and as reflected by a composite HD disease outcome [47]. Additional exploratory interim RCT only data (including Clinch Transfer Token Task and Q-motor) will be reported separately as part of the detailed intervention process analyses.

We examined balance between our three study groups (cohort, RCT intervention and control groups). Propensity score (PS) weighting methods were explored in an attempt to achieve balance on the observed characteristics of fitness, physical endurance and disease status between individuals in the RCT intervention group and those in the observational cohort with the goal of determining the feasibility of using such analyses

[4] Mean age of Enroll-HD cohort is 48.7 years [17].

[5] To access workbook, contact the Huntington Disease Society of America: https://hdsa.org/healthcare-professionals-resources/pt-continuing-education/physical-therapy/.

[6] https://www.fitabase.com/.

[7] https://enroll-hd.org/for-researchers/.

to provide evidence on the effectiveness of the intervention [48]. (Appendix 1).

Progression criteria [49] to proceed to further intervention evaluation were based on the following: over 60% drop-out from the RCT at 12 months (no progression), between 40 and 60% drop-out (changes to the intervention and/or follow-up procedures required) and less than 30% drop-out at 12 months (intervention is suitable for further evaluation without modification).

2.9. Ethics and governance

PACE-HD was sponsored by Cardiff University who retained overall responsibility for the trial. Approval was obtained from local Institutional Review Boards (IRB) or Ethics Committees at all sites and all participants signed informed consent.

3. Results

3.1. Descriptive and demographic data

Table 1 provides descriptive and demographic data across the cohort and RCT groups. Eight eight (88)% of participants were Caucasian and the remaining 12% were distributed between Black, Hispanio or Latino, American Indian, African, mixed or other.

3.2. Recruitment and retention

From February 2018 to May 2019, 274 individuals were screened. Inclusion criteria were met by 204 and 116 were enrolled for a recruitment rate of 42.3% (Fig. 1 and Appendix 2). Our targeted recruitment of 120 (60 each for RCT and cohort) was narrowly missed (116/120, 98.3%). Fifty-nine individuals were enrolled in the cohort and 57 in the RCT, however 4 individuals withdrew or were lost to follow up between recruitment and baseline assessments, reducing baseline to 112 (59 in cohort and 53 in RCT). Retention rate for 12-month follow-up for the observational cohort (51/59) was 86.4% (95% CI 75.5–93.0%) and for the RCT (45/53) was 84.9% (95% CI 73.0–92.2%). This met prespecified feasibility progression criteria of less than 30% dropout for the RCT group.

3.3. Data completeness

Data completeness (Appendices 3 & 4) was lowest for activity monitors (step counts and daily activity) and greatest for PACE-HD specific measures including predicted VO_{2max}, 6-min walk, HD-Pro-TRIAD, IPAQ and Brunel. For the PACE-HD assessments, 105/112 (93.8%) of baseline assessments were completed within the 6-week window from Enroll-HD assessments. For the 12-month assessments, 69/95 (72.6%) completed assessments ± 6 weeks from baseline. This low completion was related to scheduling issues and delays due to COVID-19-related restrictions. For the Enroll-HD assessments at 12 months, 77/83 (92.8%) were completed at ± 3 months from baseline (Appendix 5). The total number of expected exercise and falls diaries across the three RCT sites was 612, with 403 being completed (67% completion) (see Appendix 6).

Table 1
Baseline demographics and clinical assessments.

	Cohort (n = 59)	RCT control (n = 27)	RCT intervention (n = 26)
Gender Female	25(42.4%)	16(59.3%)	15(57.7%)
Age at last Enroll visit (years)	52.4(11.1)	57.1(9.8)	54.5(10.5)
BMI (kg/m2)	25.5(4.5)	25.5(4.6)	25.7(3.3)
CAG repeat length	43.1(2.4)	42.5(2.7)	43.0(3.0)
Total Motor Score (TMS)	30.8(14.9)	29.5(15.6)	30.2(18.9)
Total Functional Capacity (TFC)	10.5(2.3)	10.5(1.9)	10.4(2.0)
Medications			
HD-related motor symptoms	27(45.8%)	10(37%)	11(42.3%)
Anxiety, depression or apathy	30(50.8%)	16(59.3%)	14(53.8%)
Psychoses	0	0	3(11.5%)
Irritability	4(6.8%)	3(11.1%)	1(3.8%)
Sleep disorder	13(22%)	6(22.2%)	5(19.2%)
Beta blocker medication	6(10.2%)	1(3.7%)	1(3.8%)

Numbers are reported as mean(SD) or n(%).

3.4. Safety

Over the one-year period, 42 falls were reported in the control group [median (minimum:maximum) per participant 0 (0:9)] and 43 in the intervention group [median (minimum:maximum) per participant 0 (0:12)]. There were 8 recurrent fallers (>1 fall) in the control group and 6 in the intervention. Two control group participants attended hospital emergency rooms as a result of falls but did not require hospital admissions (thus not meeting definition of a serious adverse event (SAE)). No SAEs were reported.

3.5. Adherence

The average number of sessions completed per participant was 14.5 (5.2) (80.5%); 91.8% were conducted in-person. Adherence was prespecified as completing 10/18 intervention sessions. There were 23/26 participants who adhered to the intervention. Of the 3 non-adherers, 2 participants withdrew and the other participant was reported to be experiencing psychosocial issues that impacted their ability to engage with the intervention.

3.6. Intervention fidelity

This intervention was successfully delivered across three countries with different languages and healthcare contexts. Therapists completed a total of 63/78 (80.8%) self-report checklists evaluating intervention fidelity aligned to the intervention program theory. Therapists reported high fidelity with positive coach-participant interactions with a mean (SD) overall score (out of 4) of 3.83 (0.38) and across the domains of autonomy (3.68 (0.47)), relatedness (3.93 (0.24)) and competence (3.76 (0.47)). Additionally, therapists reported high levels of fidelity in identifying participant expectations (3.68 (0.66)) and exercise adaptation (3.56 (0.68)) but slightly less highly in communication (3.34 (1.76)) and involving family members (2.97 (1.98)). Therapists and site coordinators often needed to make multiple attempts to reach participants and/or their family members for appointment reminders, and therapists also needed to work closely with participants to implement regular physical activity within a daily routine.

Fitbit data was available for 23 out of 26 participants (partial datasets for those that withdrew were excluded from analysis). The average number of days participants had the Fitbits (i.e. could have worn the devices) was 364.9. HR was detected on an average of 269 days (75.6%) with valid wear time (≥10 h) on 219 (61.8%) days. 19/23 individuals had >70% of days where they had valid wear time.

3.7. Intervention acceptability

Twenty out of 26 intervention group participants completed an acceptability questionnaire on completion of the study. Participants reported a very high level of satisfaction with with 20/20 (100%) agreeing or strongly agreeing that they were satisfied by and enjoyed the therapist-led sessions. Further, 17/20 (85%) agreed or strongly agreed that they enjoyed sessions that were not therapist-led (independent sessions).

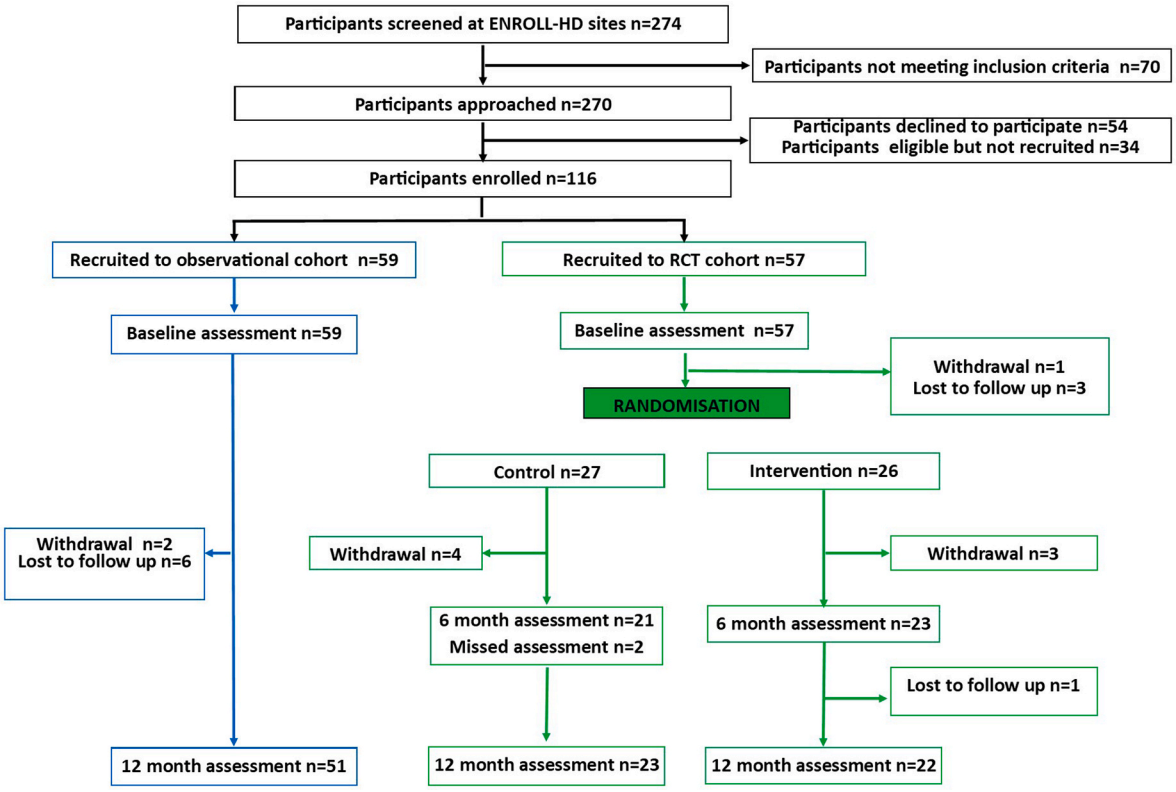

Fig. 1. CONSORT flow diagram for PACE-HD study including longitudinal cohort and nested randomized control trial (RCT).

3.8. Clinical outcomes

Table 2 provides means (SD) for the Enroll-HD and PACE-HD study assessments at baseline and 12-month follow up, and adjusted differences and 95% CI for the RCT group.

In the cohort group, rates of decline for UHDRS TMS, TFC and SDMT were similar to those reported in previous studies over a 12-month period [50]. As expected in a neurodegenerative condition, performance-based measures including predicted VO_{2max}, 6 min walk, and TUG as well as self-reported PA all declined over the 12-month period. In the RCT group, there were differences in favor of the intervention group for assessments with >60% data completion at 12 months for predicted VO_{2max}, 6-min walk, and self-reported PA (IPAQ). In an attempt to understand the differences between cohort and the 2 RCT arms for these measures, we further calculated Cohen's d effect sizes comparing differences between baseline and follow for the cohort, control and intervention groups. For the cohort group, effects sizes for VO_{2max}, 6-min walk, and IPAQ were −0.27, -.40 and -.29, indicating a small-moderate effect size suggestive of decline in all measures, as might be expected in HD. For the control group, effect sizes for the same measures respectively were −0.06, 0.07, and −0.32, indicating minimal change or small negative effect size and a somewhat smaller decline than would be expected given the degenerative nature of HD (and perhaps an indication of behavior change simply due to the nature of being monitored in the control arm). For the intervention group, effect sizes were 0.08, 0.25 and 0.07, indicating no charge or a small positive effect size, suggestive of improvement.

3.9. Mediation analysis and propensity scores

Data completeness at 6 months for the purposes of mediation analysis was comparable to that at 12 months. Structural equation modelling identified no statistically significant effects. Imbalances in pretreatment confounders (baseline fitness and endurance or disease status) for the cohort and the RCT could not be addressed via propensity score weighting due to small sample sizes.

4. Discussion

PACE-HD is the first long-term evaluation of a physical therapist-led PA intervention in individuals with HD. We successfully recruited 116 individuals with HD across three countries at 6 sites, narrowly missing our recruitment target of 120. The retention rate at 12 months was excellent particularly given that the COVID-19 pandemic adversely affected data completion over the last three months. Retention rate was greater than 80%, meeting our prespecified feasibility progression criteria. We can thus conclude that nesting a trial within a cohort such as Enroll-HD is feasible when planning long-term PA evaluation in HD. Low data completeness did, however, impact on interpretation of some important outcomes. This was particularly evident for the research-grade wearable monitors as well as several Enroll-HD extended battery measures (e.g., they were not routinely collected at some sites).

The PACE-HD intervention was safe and had high intervention fidelity, adherence and participant acceptability. We used Fitbit monitors to facilitate activity tracking and therapist coaching, which had good adherence over the 12-month intervention. Due to the individualized nature and length of the intervention, we did not summarize data about exercise uptake over the 12-month period. Previous studies have shown that aerobic and strengthening exercise three times a week for 12 weeks was effective in improving fitness and disease-specific motor function [39]. Future studies should further evaluate frequency and duration of exercise to determine any dose effects for longer term interventions.

There was a high uptake of Fitbits in the intervention group with ≥10 h wear time on >70% of days. While wearable activity monitors have been shown to be feasible in some neurodegenerative diseases [51,52] there are no published reports on the implementation of these devices in long-term PA interventions. While it is difficult to determine how often participants interacted with the devices, data from the Fitbits were used by therapists during the coaching sessions to discuss PA behavior and track progress. While there are limitations of commercial devices such as potential measurement errors [53,54], and time required to charge and sync devices, these challenges are likely to be overcome or

Table 2
Outcome measures for cohort and randomized control trial (control and intervention groups) at baseline and 12 month follow up, including adjusted mean differences and 95% CI for the randomized trial.

	Cohort (n = 59)			Randomized Control Trial (n = 53)						Control vs. Intervention	
				Control			Intervention			Adjusted differences between groups at 12 months **	Adjusted 95% CI for the difference**
		Baseline	12-month follow-up		Baseline	12-month follow-up		Baseline	12-month follow-up		
	n	Mean(SD)	Mean (SD)	n	Mean(SD)	Mean(SD)	n	Mean(SD)	Mean(SD)		
MEASURES WITH >60% DATA COMPLETENESS FOR ALL GROUPS AT 12 MONTHS											
PACE-HD measures											
Predicted VO_{2max} (ml.min-1)	49	1958.5 (759.2)	1764.3 (695.1)	20	1752.8 (729.9)	1707.3 (755.6)	19	1856.9 (587.6)	1907.9 (645.8)	105.1	(-73.5, 283.6)
6 min walk test (m)	48	503.2 (145.2)	444.8 (147.0)	20	435.0 (139.9)	444.7 (145.6)	20	417.0 (115.3)	450.1 (148.8)	21.8	(-17.7, 61.2)
IPAQ Total MET (MET minutes/wk)	37	3747.8 (3275.9)	2964.9 (2037.8)	22	3942.7 (3613.5)	2936.3 (2696.8)	18	3699.3 (2916.9)	3913.0 (3355.1)	1154.5	(-864.4,3173.5)
HD-Pro-TRIAD (total score)	49	5.9 (2.0)	5.9 (1.7)	23	6.3 (1.5)	6.2 (2.0)	22	6.7 (2.1)	6.9 (2.0)	0.5	(−0.5, 1.5)
Brunel Planned activity score	51	3.5 (1.2)	3.8 (1.0)	23	3.6 (1.1)	3.6 (1.0)	21	3.2 (1.2)	3.8 (0.8)	0.3	(−0.3, 0.8)
Brunel Unplanned activity score	51	2.6 (0.8)	2.3 (0.7)	23	2.5 (0.7)	2.8 (0.6)	21	2.9 (0.7)	2.7 (0.8)	−0.1	(−0.5, 0.4)
Enroll-HD UHDRS Motor & Functional											
UHDRS Total Motor Score (TMS)	48	31.0 (14.7)	33.6 15.9)	18	24.8 (14.1)	29.2 (14.7)	16	25.8 (16.2)	28.6 (16.9)	−2.1	(−6.6, 2.5)
UHDRS Total functional capacity (TFC)	48	10.4 (2.3)	9.4 (2.4)	19	10.4 (2.0)	9.9 (2.3)	16	11.0 (1.6)	10.5 (1.5)	0	(−0.7, 0.7)
UHDRS Functional assessment score	48	21.8 (3.2)	21.3 (3.2)	18	20.6 (4.1)	19.9 (3.7)	16	22.3 (2.2)	21.2 (2.2)	0.3	(−0.8, 1.3)
UHDRS Independence score (%)	48	85.4 (11.0)	81.4 (9.6)	19	86.3 (10.3)	83.4 (11.3)	16	86.6 (9.6)	83.1 (7.7)	−0.1	(−4.8, 4.7)
Enroll HD Behavioral											
PBA: Irritability aggression score	48	1.3 (3.0)	2.1 (4.0)	19	2.6 (4.0)	2.5 (2.8)	16	3.9 (3.8)	3.1 (2.7)	−0.1	(−1.9, 1.6)
PBA: Psychosis score	48	0.0 (0.1)	0.1 (0.6)	19	0.0 (0.0)	0.0 (0.0)	16	0.0 (0.0)	0.1 (0.3)	0.1	(−0.1, 0.2)
PBA: Apathy score	48	2.7 (3.9)	2.1 (3.3)	19	2.5 (3.4)	3.3 (3.2)	16	4.6 (4.3)	3.5 (2.9)	−1.1	(−3.0, 0.8)
PBA: Depression score	48	2.8 (4.4)	3.3 (5.1)	19	3.2 (3.7)	3.3 (3.3)	16	5.4 (6.1)	5.7 (7.2)	0.9	(−1.6, 3.5)
PBA: Executive function score	48	3.0 (4.5)	2.0 (3.9)	19	1.6 (2.3)	3.0 (3.6)	16	4.2 (4.8)	2.4 (3.1)	−2.1	(−4.3, 0.1)
MEASURES WITH <60% DATA COMPLETENESS FOR ALL GROUPS AT 12 MONTHS											
PACE-HD measures											
Accelerometer-derived average weekly steps	26	8363.5 (3779.7)	8192.9 (4418.2)	3	11331.0 (5283.0)	9012.7 (3597.0)	5	8132.5 (2784.4)	5752.3 (3315.6)		
Accelerometer-derived average weekly activity	27	50.1 (18.6)	49.7 (23.6)	4	45.1 (4.6)	61.3 (36.0)	5	45.5 (7.3)	34.4 (19.3)		
Enroll-HD Behavioral Measures											
HAD-SIS: Anxiety sub score	18	3.8 (4.3)	3.8 (4.7)	15	4.3 (2.8)	4.1 (2.9)	11	6.5 (4.1)	7.0 (4.0)		
HAD-SIS: Depression sub score	18	4.1 (3.7)	3.2 (3.7)	15	4.8 (3.0)	3.8 (2.9)	11	5.6 (4.3)	5.0 (4.4)		
HAD-SIS: Irritability sub score	18	3.0 (3.6)	3.1 (3.4)	15	3.8 (3.6)	3.8 (3.3)	11	7.3 (5.0)	7.6 (4.8)		
Enroll-HD Cognitive Measures											
Symbol Digit Modality Test (# correct)	46	30.7 (12.0)	28.5 (11.8)	19	25.9 (13.5)	26.5 (13.1)	15	28.7 (13.3)	29.3 (12.1)		
Stroop Word Reading (# correct)	46	69.9 (24.1)	63.1 (22.0)	19	64.0 (24.9)	62.3 (21.2)	15	70.5 (16.5)	64.7 (18.2)		
Stroop Colour Naming (# correct)	47	50.4 (17.5)	48.2 (16.1)	19	45.7 (16.0)	45.9 (18.2)	15	48.9 (14.8)	46.7 (14.9)		
Stroop Interference (# correct)	44	28.9 (12.2)	26.9 (12.2)	17	26.4 (12.3)	24.7 (11.0)	15	25.5 (12.0)	26.4 (9.1)		
Verbal and Category Fluency (# correct)	47	16.4 (5.4)	15.8 (6.1)	19	13.8 (5.9)	13.5 (4.6)	15	16.0 (5.1)	16.8 (6.7)		
Trail making Test: Part A (sec)	45	50.4 (31.2)	49.5 (26.8)	18	50.4 (24.5)	47.4 (20.7)	14	49.1 (20.2)	42.4 (17.6)		
Trail making Test: Part B (sec)	45	114.5 (62.4)	130.2 (71.0)	15	110.8 (62.5)	100.4 (54.4)	14	125.8 (75.8)	121.2 (55.5)		
Enroll-HD Physical Therapy Measures											
Timed Up & Go (sec)	33	8.9 (2.4)	10.3 (8.5)	16	9.1 (3.4)	8.6 (4.0)	13	7.9 (1.6)	7.4 (1.3)		
30 s chair stand test (# repetitions)	33	12.6 (4.4)	12.5 (3.8)	13	13.0 (4.2)	13.2 (5.6)	12	11.2 (3.2)	12.9 (2.7)		
ENROLL-HD Quality of Life											

(*continued on next page*)

Table 2 (*continued*)

	Cohort (n = 59)			Randomized Control Trial (n = 53)						Control vs. Intervention	
				Control			Intervention			Adjusted differences between groups at 12 months **	Adjusted 95% CI for the difference**
		Baseline	12-month follow-up		Baseline	12-month follow-up		Baseline	12-month follow-up		
	n	Mean(SD)	Mean (SD)	n	Mean(SD)	Mean(SD)	n	Mean(SD)	Mean(SD)		
SF12: Physical Component (PCS)	29	50.9 (6.9)	51.7 (5.6)	17	49.4 (7.8)	48.2 (6.5)	12	48.8 (6.0)	50.9 (5.3)		
SF12: Mental Component (MCS)	29	52.7 (9.1)	51.2 (9.7)	17	51.9 (5.8)	51.1 (10.8)	12	44.9 (12.6)	44.3 (12.5)		
Composite UHDRS	45	10.5 (3.6)	9.3 (3.5)	18	10.1 (3.9)	9.5 (4.0)	15	11.0 (3.2)	10.2 (3.0)		

IPAQ: International Physical Activity Questionnaire. **HD-PRO-TRIAD:** range 3–15, with higher scores indicating worse HD-related symtpoms. **Brunel Planned and Unplanned Physical Activity:** dimensions are calculated by adding scores from items 1–6 (planned) and 7–9 (unplanned), then dividing them by six and three, respectively. Factor scores ranged from 1.00 to 5.00, with higher scores indicating higher engagement in PA. **UHDRS (**Unified Huntington's Disease Rating Scale): range 0–124, higher score indicates worse motor symptoms. **TFC (**Total Functional Capacity): range 0–13, 13 indicates highest functioning. **Independence Score:** range 0–25, 25 = independent. **PBA (**Problem Based Assessment): ranges - irritability and aggression 0–32; psychosis 0-32; apathy 0–16; depression 0–48; executive function 0–32; higher scores indicate worse behavioral function. **HAD-SIS (**Hospital Anxiety and Depression Scale): anxiety and depression subscales range 0–21; irritability subscale 0–24. **SF-12 (**12-item Short Form Survey) reported as t scores; higher scores indicate higher functioning. **Enroll-HD Composite UHDRS** lower scores indicate higher functioning.

*mean(Intervention) – mean(Control).

**Differences & 95% CI adjusted for baseline measure and all minimization variables (age, gender, TMS). VO2max is adjusted for only TMS.

minimized as technology develops.

Our study design included a cohort group receiving no contact with study personnel over the year as well as a control group who received monthly contact to facilitate completion of exercise and falls diaries and also completed a 6-month assessment. Our results suggest that individuals in the control group may have benefited from being in a clinical trial and reflecting on exercise and activity each month, as evidenced by the lack of decline in some measures of physical fitness and physical activity compared to the cohort. Future exercise studies should consider the potential benefits for participants of being in a "control" group, especially in complex diseases such as HD.

Clinical studies of short-term exercise interventions have demonstrated improvements in fitness, motor impairment and quality of life in people with HD [5,55]. Longer term pragmatic evaluations of well-defined exercise interventions are challenging to set up and deliver, particularly in rare diseases. Embedded trials within cohorts [56] provide an efficient method for recruitment, and may reduce burden through the use of routinely collected prospective outcome data. Such designs are most suited to open trials and comparisons to treatment as usual, which may introduce elements of assessor bias. The inclusion of measures less subject to investigator bias, including wearable technologies for the assessment of PA and utilizing quantitative motor and cognitive assessments, is therefore crucial. While we attempted to include such measures in the form of wearable devices (research grade accelerometers), the poor completion rate at follow-up limited our ability to analyze these data. Future studies should implement additional methods to ensure data completeness for wearable devices.

While imbalances in pretreatment confounders for the cohort and the RCT could not be addressed via propensity score weighting due to limited sample size, there is still promise in the potential use of this approach to allow for more robust analyses comparing an observational cohort to an RCT intervention group. Capitalizing on an existing cohort will remove the type of control group bias seen in this study when comparing the control group from the RCT to the intervention group, and it allows for additional layers of understanding about the potential effects of new interventions for individuals. As shown by Markoulidakis et al. [48], at least 60 individuals per treatment group per confounding covariate are required to estimate high quality propensity score weights; this would be achievable if nesting a trial within a large cohort such as Enroll-HD.

Nesting trials within cohorts may offer a number of benefits for trials research in the HD community; removing the need to specifically consent those randomized into the control arm to act as an intervention comparator can reduce the potential Hawthorne effect, particularly in studies where blinding is not possible. The Enroll-HD study provides an ideal platform for conducting such studies. The addition of outcomes measures for the evaluation of specific factors relevant to the intervention being studied (for example measures of fitness when evaluating PA interventions) may be needed and study teams need to plan for the resource and time requirements to facilitate data linkage to the cohort.

As a feasibility study, this study was not designed to assess efficacy and outcomes should be interpreted with caution. While the intervention and study design was feasible, there are numerous challenges in implementing physical therapy-led interventions in people with HD. Apathy and amotivation can impact adherence and engagement in exercise routines [57], and individuals in all groups had some degree of apathy, anxiety and depression, as measured by the PBA and HAD-SIS, although values were generally within the normal or low normal range. While beyond the scope of this paper, secondary analyses from this trial will explore the relationship of these and other factors to clinical outcomes. Furthermore, the number of falls remained relatively constant over the 1 year period for both the control and intervention groups. Importantly, this study was not designed to address falls specifically but was focused on increasing real-world physical activity. As participants in the intervention group had a concomitant increase in physical activity that did not result in increased falls or injuries, we view this as suggesting that physical activity can be conducted safely in this population, and future studies should specifically address individual fall risk mitigation.

There were further challenges in implementing this trial with regards to data completeness as well as conducting the assessments within predefined windows, which were exacerbated by the onset of the COVID-19 pandemic towards the end of the study. Additionally, there were clear challenges in collecting digital data and data transfer from the sites resulting in poor return rates. Such challenges should be considered in future studies, and efforts to minimize site burden with regards to digital data should be implemented.

4.1. Summary

We have shown that it is possible to deliver and evaluate a long-term physical therapist-led intervention in people with HD. We have further demonstrated the feasibility of a nested trial within cohort design, that brings with it potential advantages in efficiency and generalizability,

providing study teams carefully consider the complexity and associated challenges. Harnessing the potential of cohort-based studies is the next critical step in progressing the evidence in support of non-pharmacological life-style interventions in HD disease management.

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Declaration of interest

Monica Busse is a member of the STEMM1 (Medicine and Medical Sciences) Learned Society Scrutiny committee, NIHR HTA Commissioning Funding panel, NIHR Clinical Trials Unit Standing Advisory Committee, Advisory board for Health and Care Economics Cymru (HCEC), Invited member DHSC/UKRI COVID-19 rapid response rolling call – College of Experts, Member of the global Enroll-HD Scientific Planning Committee, and European Huntington's Disease Network (EHDN) Clinical Trials Taskforce. Received honoraria from CHDI and grants from National Institute for Health Research, Alzheimer Society, Jacques and Gloria Gossweiler Foundation, and Health and Care Research Wales.

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In January 2021, Google purchased Fitbit and is now the parent company of the study sponsor. Ciaran Friel, a co-investigator of this study, has a family member that owns stock in Google.

Anne Rosser is Chair of the executive committee of the European Huntington Disease Network (EHDN), which is funded by CHDI Foundation, with remuneration paid to Cardiff University, and is chair and trustee of the Guarantors of Brain charity. She is European co-PI for the Prilenia PROOF-HD trial, with remuneration paid to Cardiff University, and provides consultancy and/or advisory board membership for Roche, Wave pharmaceuticals, Novartis and Triplet Therapeutics. She has obtained research grants from the UK MRC, Health and Care Research Wales, and EU Horizon.

Robin Schubert is employed by QuantiMedis GmbH, a service provider for the quantitative assessment battery "Q-motor" which was used in this study.

Beth Ann Griffin, Cheney Drew, Mark Kelson, Katy Hamana, Rebecca Playle, Katie Taiyari, Rhys Williams-Thomas and Philippa Morgan-Jones have no disclosures.

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Appendix 1

Technical analysis

Technical Appendix on Propensity Score Weighting

Propensity score (PS) weighting methods were explored in an attempt to achieve balance on the observed characteristics fitness, physical endurance and disease status between individuals in the RCT intervention group and those in the observational cohort in the absence of randomization [48]. The goal of using PW weighting was to determine the feasibility of using such analyses to provide evidence on the effectiveness of the intervention [48].

More specifically, we carefully examined balance between our three study groups (the cohort and RCT groups) to assess the comparability between the RCT groups and how similar the cohort group was when compared to the intervention group from the RCT. We only considered VO_{2max} to be the outcome of primary interest for this exploratory work. Balance was assessed on the participant characteristics used to minimize bias in the RCT (Age, Gender, TMS and baseline VO_{2max}) alongside Body Mass Index (BMI) and CAG repeat length.We computed both standardized mean differences (SMD) to assess differences on the means between the groups and Kolmogorov-Smirnoff (KS) Statistics to assess differences in the distributions of the key confounders. For both, we considered anything >0.1 to denote a potentially meaningful imbalance [58]..

Table A1 provides descriptive and demographic data across the cohort and RCT groups as well as detailed information about the balance achieved in the study prior to using PS weights. First, as shown, there were a few notable differences between the RCT groups where the standardized mean differences were greater than 0.1. Namely, Age, and CAG length repeat have SMD over 0.1. Especially for AGE, this was notable, as it was one of the characteristics the individuals were randomized on in the RCT. However, this type of difference is not unexpected given the small sample size; the limitations imposed by the sample size (30 individuals were assigned to each treatment group) made it challenging to perfectly randomized the

participants. Additionally, Age, TMS, BMI, and CAG repeat length differed significantly across the two RCT groups when considering the entire distributions (KS statistics over 0.1). TMS, which was another characteristic considered in the randomization process, had low SMD but large KS statistics. Ultimately, we had strong evidence of imbalances in the two RCT groups and this motivated our attempt to use PS weights to remove these imbalances.

Next, there were also notable differences between the observational cohort and the RCT intervention group with large SMD on Age and Gender (Gender SMD is exceptionally large – 0.5), and significant differences in KS statistic (all statistics over 0.1). Theoretically, PS weights could be deployed to control for confounding bias for all these covariates and thus we attempted to estimate PS weights for comparing the observational control cohort to the RCT intervention group. Unfortunately, our work was again greatly limited by the sample sizes of the groups. As noted in Markoulidakis et al. [58] (2020), a study should ideally have at least 60 individuals per treatment group per confounding covariate to be able to estimate PS weights well. This would mean, to control for four covariated we require 60x4 = 240 individuals per treatment group to attempt balance via PS weights) – to a total sample of at least 480 individuals.

Table A1
Baseline demographics and clinical assessments along with balance information

	Treatment Group	RCT Control Group			Observational Control Cohort		
	Mean	Mean	SMD	KS	Mean	SMD	KS
Gender (%F)	57.7	59.3	0.14	0.07	42.4	0.18	0.09
Age	54.5	57.1	0.25	0.15	52.4	0.17	0.17
TMS	30.2	29.5	0.03	0.16	30.8	0.04	0.12
BMI	25.7	25.5	0.08	0.18	25.5	0.08	0.21
CAG length	43	42.5	0.19	0.11	43.1	0.08	0.16
VO_{2max}	1856.87	1752.76	0.18	0.34	2033.27	0.30	0.38

Note – SMD and KS compare the RCT control group and observational control cohort to the RCT treatment group.

Fig. 1 shows the performance of the propensity score weighting for both the RCT and cohort on SMDs and KS. The PS weights, do not achieved adequate balance between the treatment groups, for the baseline covariates, neither in term of SMD, nor KS (some SMD and KS values are above 0.1). The level of balance achieved as measured by the KS statistic was not sufficient since the values were largely above the 0.1 threshold. Of note, the KS statistics were 0.16 for both TMS and VO_{2max} for the comparison of the observational control cohort and the RCT intervention group and 0.18 for the comparison of the two RCT groups. Such large imbalances between the distributions of the baseline covariates of the treatment groups, provided evidence that the PS weights could not control for confounding bias from observed key confounders. Thus, any estimation of the causal treatment effect would be biased when using these PS weights. As noted above, the cut-point for having good balance after PS weighting for both the SMD and KS statistics is a level of 0.1 or less; this is what is required to consider the groups as adequately balanced and that it would be reasonable to proceed with estimate treatment effects because achieving such balance is a good indication that the confounding bias is eradicated [58].

Given the lack of balance achieved, we did not pursue outcome analyses for the PS weighted samples.

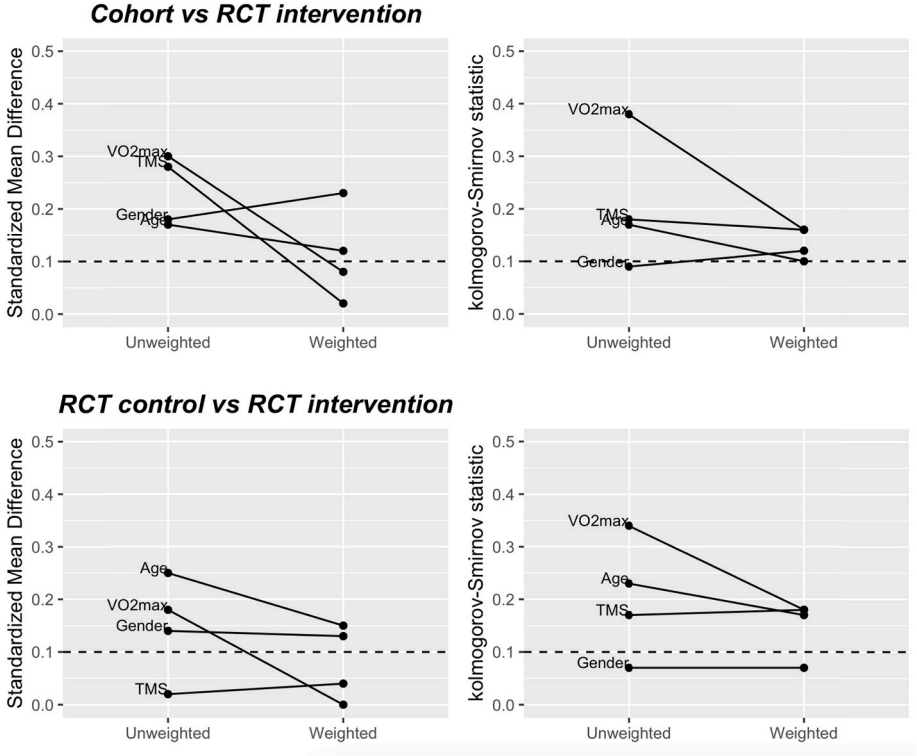

Fig. A1. SMD (left) and KS statistic (right) for the observational cohort versus the RCT intervention (top subfigures) and the RCT control versus RCT intervention (lower subfigures). The plots depict how the balance of the baseline covariates (VO2max and TMS) changes when using PS and balancing weights to control for confounding bias. PS and balancing weights were used to create pseudo-populations that were balanced between the treatment groups, thus one typically expects the balance to improve after weighting. The black horizontal dashed-line represents the balance level 0.1. To consider that a weighted sample is adequately balanced, all covariates should report post-weighing KS statistics and SMDs below 0.1 (below the black horizontal dashed-line). In this sample, the balance achieved used PS weights was not considered adequate.

Appendix 2

Supplementary screening and recruitment

Participants failed screening n=70.
Inclusion #1 (diagnosis of HD confirmed by genetic testing) = 9.
Inclusion #3 (current participant on Enroll-HD) = 9.
Inclusion #4 (up to stage 2 disease [TFC7-13]) = 33.
Exclusion #1 (diagnosis of juvenile onset HD) = 1.
Exclusion #2 (history of co-morbid neurological condition) = 1.
Exclusion #3 (acute orthopaedic condition) = 1.
Exclusion #4 (inability/unwillingness to provide consent) = 3.
Uses walking frame = 1.
Other illness = 4.
DBS implant = 1.
Not given = 7.
Eligible but not recruited n=34.
No response to invite = 5.
Enroll-HD visit not scheduled in time n = 22.
Transferred to another Enroll site = 4.
Missed Enroll visit = 3.
Declined to participate n=54.
Takes too long/too many visits = 6.
Not interested in study = 27.
Personal reasons = 1.
Ongoing illness = 1.
Scheduling conflicts = 2.
Clashes with work = 1.
Can't tolerate sensor at night = 1.
Not up to it = 2.
Travel too difficult = 10.
Waiting for other study (Roche) = 1.
Prefer exercise without support = 1.
Not specified = 1.

Appendix 3

Data completeness of the cohort

Appendix Table 3
Data Completeness of the Cohort (n = 59)

	Available at baseline n(%)	Available at 12 month follow-up n(%)	Available at both baseline and 12 month follow-up n(%)
MEASURES WITH >60% DATA COMPLETENESS AT 12 MONTHS			
PACE-HD measures			
Predicted VO2 max	56(94.9)	50(84.7)	49(83.05)
6 min walk	56(94.9)	50(84.7)	48(81.36)
HD-Pro Triad	57(96.6)	50(84.7)	49(83.05)
IPAQ Total MET	52(88.1)	42(71.2)	37(62.71)
Brunel Planned activity score	58(98.3)	51(86.4)	51(86.4)
Brunel Unplanned activity score	58(98.3)	51(86.4)	51(86.4)
Enroll-HD UHDRS Motor & Functional			
UHDRS Total Motor Score (TMS)	59(100.0)	48(81.4)	48(81.4)
UHDRS Total functional capacity (TFC)	59(100.0)	48(81.4)	48(81.4)
UHDRS Functional assessment score	59(100.0)	48(81.4)	48(81.4)
UHDRS Independence score	59(100.0)	48(81.4)	48(81.4)
Enroll HD Behavioral			
PBA: irritability aggression score	59(100.0)	48(81.4)	48(81.4)
PBA: Psychosis score	59(100.0)	48(81.4)	48(81.4)
PBA: Apathy score	59(100.0)	48(81.4)	48(81.4)
PBA: Depression score	59(100.0)	48(81.4)	48(81.4)
PBA: Executive function score	59(100.0)	48(81.4)	48(81.4)
MEASURES WITH <60% DATA COMPLETENESS AT 12 MONTHS			
PACE-HD			
Accelerometer-derived average weekly steps	43(72.9)	22(37.3)	18(30.51)
Accelerometer-derived average weekly activity	49(83.1)	30(50.8)	27(45.76)
Enroll-HD Behavioral Measures			
HAD-SIS: Anxiety subscore	32(54.2)	25(42.4)	18(30.51)
HAD-SIS: Depression subscore	32(54.2)	25(42.4)	18(30.51)

(*continued on next page*)

Appendix Table 3 (*continued*)

	Available at baseline n(%)	Available at 12 month follow-up n(%)	Available at both baseline and 12 month follow-up n(%)
HAD-SIS: Irritability subscore	32(54.2)	25(42.4)	18(30.51)
HAD-SIS: Outward irritability subscore	32(54.2)	25(42.4)	18(30.51)
HAD-SIS: Inward irritability subscore	32(54.2)	26(44.1)	19(32.20)
Enroll-HD Cognitive Measures			
Symbol Digit Modality Test	58(98.3)	47(79.7)	46(77.97)
Stroop Word Reading	58(98.3)	47(79.7)	46(77.97)
Stroop Colour Naming	59(100.0)	47(79.7)	47(79.66)
Stroop Interference	57(96.6)	46(78.0)	44(74.58)
Verbal and Category Fluency	58(98.3)	47(79.7)	47(79.66)
Trail making Test: Part A	58(98.3)	46(78.0)	45(76.27)
Trail making Test: Part B	58(98.3)	46(78.0)	45(76.27)
Enroll-HD Physical Therapy Measures			
Timed Up & Go	43(72.9)	35(59.3)	33(55.93)
30 s chair stand test	43(72.9)	35(59.3)	33(55.93)
ENROLL-HD Quality of Life			
SF12: Physical Component (PCS)	47(79.7)	35(59.3)	29(49.15)
SF12: Mental Component (MCS)	47(79.7)	35(59.3)	29(49.15)

Appendix 4

Data completeness of randomized controlled trial

Data Completeness of the Randomized Controlled Trial (RCT) (Intervention n = 26; Control n = 27)								
	Available at baseline		Available at 6 month follow-up		Available at 12 month follow-up		Available at both baseline and 12 month follow-up (complete cases)	
	Intervention n (%)	Control n (%)	Intervention n (%)	Control n (%)	Intervention n (%)	Control n (%)	Intervention n (%)	Control n (%)
MEASURES WITH >60% DATA COMPLETENESS at 12 MONTHS								
PACE-HD measures								
Predicted VO2 max	26(100.00)	27(100.00)	26(100.00)	27(100.00)	19(73.08)	20(74.07)	19(73.08)	20(74.07)
6 min walk	26(100.00)	27(100.00)	21(80.77)	18(66.67)	20(76.92)	20(74.07)	20(76.92)	20(74.07)
HD-Pro Triad data	26(100.00)	27(100.00)	26(100.00)	27(100.00)	22(84.62)	23(85.19)	22(84.62)	23(85.19)
IPAQ	26(100.00)	27(100.00)	14(53.85)	16(59.26)	18(69.23)	22(81.48)	18(69.23)	22(81.48)
Brunel Planned activity score	26(100.00)	27(100.00)			21(80.77)	23(85.19)	21(80.77)	23(85.19)
Brunel Unplanned activity score	26(100.00)	27(100.00)			21(80.77)	23(85.19)	21(80.77)	23(85.19)
Enroll-HD UHDRS Motor & Functional								
UHDRS Total Motor Score (TMS)	26(100.00)	27(100.00)			16(61.54)	18(66.67)	16(61.54)	18(66.67)
UHDRS Total functional capacity (TFC)	26(100.00)	27(100.00)			16(61.54)	19(70.37)	16(61.54)	19(70.37)
UHDRS Functional assessment score	26(100.00)	26(96.30)			16(61.54)	18(66.67)	16(61.54)	18(66.67)
UHDRS Independence score	26(100.00)	27(100.00)			16(61.54)	19(70.37)	16(61.54)	19(70.37)
Enroll HD Behavioral								
PBA: irritability aggression score	26(100.00)	27(100.00)			16(61.54)	19(70.37)	16(61.54)	19(70.37)
PBA: Psychosis score	26(100.00)	27(100.00)			16(61.54)	19(70.37)	16(61.54)	19(70.37)
PBA: Apathy score	26(100.00)	27(100.00)			16(61.54)	19(70.37)	16(61.54)	19(70.37)
PBA: Depression score	26(100.00)	27(100.00)			16(61.54)	19(70.37)	16(61.54)	19(70.37)
PBA: Executive function score	26(100.00)	27(100.00)			16(61.54)	19(70.37)	16(61.54)	19(70.37)
MEASURES WITH <60% DATA COMPLETENESS AT 12 MONTHS								
PACE-HD								
Accelerometer-derived average weekly steps	11(42.31)	12(44.44)	7(26.92)	2(7.41)	5(19.23)	6(22.22)	4(15.38)	3(11.11)
Accelerometer-derived average weekly activity	26(100.00)	27(100.00)	26(100.00)	27(100.00)	25(96.15)	26(96.30)	25(96.15)	26(96.30)
Enroll-HD Behavioral Measures								
HAD-SIS: Anxiety subscore	25(96.15)	26(96.30)			11(42.31)	16(59.26)	11(42.31)	15(55.56)
HAD-SIS: Depression subscore	25(96.15)	26(96.30)			11(42.31)	16(59.26)	11(42.31)	15(55.56)
HAD-SIS: Irritability subscore	25(96.15)	26(96.30)			11(42.31)	16(59.26)	11(42.31)	15(55.56)
HAD-SIS: Outward irritability subscore	25(96.15)	26(96.30)			11(42.31)	16(59.26)	11(42.31)	15(55.56)
HAD-SIS: Inward irritability subscore	25(96.15)	26(96.30)			11(42.31)	16(59.26)	11(42.31)	15(55.56)
Enroll-HD Cognitive Measures								
Symbol Digit Modality Test	23(88.46)	27(100.00)			16(61.54)	19(70.37)	15(57.69)	19(70.37)
Stroop Word Reading	25(96.15)	27(100.00)			16(61.54)	19(70.37)	15(57.69)	19(70.37)
Stroop Colour Naming	25(96.15)	27(100.00)			16(61.54)	19(70.37)	15(57.69)	19(70.37)
Stroop Interference	25(96.15)	25(92.59)			16(61.54)	19(70.37)	15(57.69)	17(62.96)
Verbal and Category Fluency	25(96.15)	27(100.00)			16(61.54)	19(70.37)	15(57.69)	19(70.37)
Trail making Test: Part A	25(96.15)	27(100.00)			15(57.69)	18(66.67)	14(53.85)	18(66.67)
Trail making Test: Part B	24(92.31)	25(92.59)			15(57.69)	17(62.96)	14(53.85)	15(55.56)
Enroll-HD Physical Therapy Measures								

(*continued on next page*)

(*continued*)

Data Completeness of the Randomized Controlled Trial (RCT) (Intervention n = 26; Control n = 27)								
	Available at baseline		Available at 6 month follow-up		Available at 12 month follow-up		Available at both baseline and 12 month follow-up (complete cases)	
	Intervention n (%)	Control n (%)	Intervention n (%)	Control n (%)	Intervention n (%)	Control n (%)	Intervention n (%)	Control n (%)
Timed Up & Go	24(92.31)	24(88.89)			13(50.00)	16(59.26)	13(50.00)	16(59.26)
30 s chair stand test	24(92.31)	24(88.89)			12(46.15)	13(48.15)	12(46.15)	13(48.15)
ENROLL-HD Quality of Life								
SF12: Physical Component (PCS)	23(88.46)	24(88.89)			12(46.15)	18(66.67)	12(46.15)	17(62.96)
SF12: Mental Component (MCS)	23(88.46)	24(88.89)			12(46.15)	18(66.67)	12(46.15)	17(62.96)
RCT ONLY DATA								
Q-motor	15(57.69)	14(51.85)			15(71.42)	14(60.87)	unavailable	unavailable
C3T data	26(100.00)	27(100.00)	22(84.62)	19(70.37)	N/A*	N/A*	N/A*	N/A*
Lorig data	26(100.00)	27(100.00)	23(88.46)	20(74.07)	18(69.23)	13(48.15)	18(69.23)	13(48.15)

*C3T was only assessed at baseline and 6 months.

Appendix 5

Summary of data collection completed within prespecified windows

	Baseline PACE-HD & Enroll-HD Data collection within ± 6 week window	6 month PACE-HD Data collection 6 months ± 2 weeks from baseline PACE-HD	12 month PACE-HD Data collection 12 months ± 6 weeks from baseline PACE-HD	12 month Enroll-HD Data collection 12 months ± 3 months from baseline ENROLL-HD
RCT				
Site 1a	16/16 (100%)	15/16 (93.8%)	15/16 (93.8%)	16/16 (100%)
Site 1b	7/7 (100%)	5/5 (100%)	3/5 (60.0%)	5/5 (100%)
Site 2	11/13 (84.6%)	8/10 (80.0%)	10/10 (100%)	7/9 (77.8%)
Site 3	13/17 (76.5%)	10/13 (76.9%)	6/14 (42.9%)	5/5 (100%)
Total	47/53 (88.7%)	38/44 (86.4%)	34/45 (75.6%)	33/35 (94.3%)
Cohort				
Site 4	20/20 (100%)		16/18 (88.9%)	16/16 (100%)
Site 5	18/18 (100%)		12/17 (70.6%)	16/17 (94.1%)
Site 6	20/21 (95.2%)		7/15 (46.7%)	12/15 (80.0%)
Total	58/59 (98.3%)		35/50 (70.0%)	44/48 (91.7%)

In both ENROLL and PACE window at 12 months	
RCT 12 months	
Site 1a	15/16 (93.8%)
Site 1b	3/5 (60.0%)
Site 2	6/9 (66.7%)
Site 3	1/6 (16.7%)
Total	25/36 (69.4%)
Cohort 12 month	
Site 4	14/16 (87.5%)
Site 5	11/17 (64.7%)
Site 6	6/14 (42.9%)
Total	31/47 (66.0%)

Data represented as number of participants where assessments took place within respective windows compared to number of participants who attended at each time point. Pre-specified data collection windows were/- 6 weeks for conducting PACE-HD and Enroll-HD assessments at baseline and 12 months; 6 months±2 weeks from conducting baseline assessment for PACE-HD assessments at 6 months; and 12 months ± 3 months from conducting baseline Enroll-HD assessments for Enroll-HD assessments at 12 months. Denominators based on those participants who attended at each time point.

Appendix 6

Falls and Exercise Diary Completion

	Intervention Site 1	Intervention Site 2	Intervention Site 3	Overall
	N or n/n (%)	N or n/n (%)	N or n/n (%)	N or n/n (%)
Total diaries returned	264	144	204	612
Proportion of diaries completed	211 (80%)	58 (40%)	134 (66%)	403 (67%)

Appendix 7

Enroll-HD Periodic Dataset 5. Acknowledgement list

The acknowledgement list contains study site staff who have actively contributed to Enroll-HD at the different study sites.

study site	country	name
ColumbiaUniv	USA	Arthur Gillman
ColumbiaUniv	USA	Ashwini Rao
ColumbiaUniv	USA	Carol Moskowitz
ColumbiaUniv	USA	Elan Louis
ColumbiaUniv	USA	Hiral Shah
ColumbiaUniv	USA	Karen Marder
ColumbiaUniv	USA	Kiryung Kim
ColumbiaUniv	USA	Lori Quinn
ColumbiaUniv	USA	Masood Manoochehri
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ColumbiaUniv	USA	Patrick Einhorn
ColumbiaUniv	USA	Paula Wasserman
ColumbiaUniv	USA	Ronda Clouse
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UnivHospUlm	Germany	Michael Orth
UnivHospUlm	Germany	Moreen Igbineweka
UnivHospUlm	Germany	Panteha Fathinia
UnivHospUlm	Germany	Patrick Weydt
UnivHospUlm	Germany	Sonja Trautmann
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