Exploring the feasibility of a novel and efficient trial design for the evaluation of long-term **P**hysical **AC**tivity and **E**xercise outcomes in people with **H**untington's **D**isease.

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BACKGROUND

- Evidence of best practice for long term physical activity in Huntington's disease (HD) is poor
- Shorter term interventions (up to 12 weeks) provide support for physical activity in terms of motor function as well as a range of physical and social benefits
- Longer-term multi-disciplinary interventions involving physical and occupational therapy delivered through inpatient settings have reported positive outcomes
- A consultation model (where therapists support community engagement in physical activity over the longer term) requires evaluation
- Conducting large-scale, longer-term evaluations of physical activity is challenging, not least due to competitive recruitment to high priority pharmacological trials
- Exploring ways to use existing data for evaluation of non-drug interventions is a priority
- We investigated the feasibility of nesting randomized controlled trial of a physical activity coaching intervention within Enroll-HD, an established HD cohort study

METHODS

- Study design: A "Trial within a Cohort" (TWiC) to compare a physical activity intervention with usual activity in individuals with early-mid stage HD
- Recruitment target: 120 participants across seven Enroll-HD (https://enroll-hd.org/) sites
- Three sites served as observational sites only, four sites conducted the nested RCT
- Inclusion criteria: 1) confirmed genetic diagnosis of HD
  2) over 18 years of age
  3) currently registered as a participant in Enroll-HD
  4) ≤ stage 2 disease status (i.e. total functional capacity 7-13)
- The primary outcome was feasibility defined by recruitment, retention, data completeness, adherence, fidelity and acceptability
- Demographic and disease-specific measures were obtained through linkage with the Enroll-HD dataset
- Exploration of effect estimates for long-term physical activity in HD compared to usual activity were secondary outcomes
- Propensity score (PS) weighting methods were used in an attempt to achieve balance in fitness, physical endurance and disease status between individuals in the RCT intervention group and those in the observational cohort in the absence of randomisation

For further information (via QR code) on PS approach *see Markoulidakis et al. Examining the effect of exercise on the progression and severity of Huntington's disease using different covariate balancing methods and simulated data derived from the PACE-HD study*.

INTERVENTION

- PACE-HD is a theoretically informed physical activity behavioural change intervention based on knowledge developed in Exert-HD and Engage-HD
- The intervention was mapped using a logic model and consisted of 18 face-to-face, 1:1 physical therapy sessions with a qualified physical therapist over 12 months (Figure 1)
- A disease-specific workbook (available in English, German and Spanish; Figure 2) supported discussions and goal setting
- Participants decided timing, location and nature of sessions (in consultation with their therapist)
- Participants were given Fitbits (Charge 2) to be used throughout the 12-month study

Figure 1: The PACE-HD Activity Pyramid

Figure 2: PACE-HD workbook (German)

RESULTS

- 116 participants (56♀) from the USA, Spain and Germany were recruited (see Table 1)
- Figure 3 describes the flow of participants in both the RCT and the cohort
- There were imbalances at baseline for gender, age, BMI and CAG (as assessed by Standardized Mean Difference (SMD) (*a* – SMD >0.1) and Kolmogorov-Smirnov (KS) statistic (*b* – KS>0.1)) both in the control and the observational cohort when compared with the intervention group (Table 1)

Table 1: Characteristics of all participants at baseline

	RCT intervention (n=26)	RCT control (n=27)	Cohort (n=59)
Gender %F	15 (57.7%)	16 (59.3%)	25 (42.4%) ^{a,b}
Mean (SD) age at last Enroll visit (years)	54.5 (10.5)	57.1 (9.8) ^{a,b}	52.4 (11.1) ^{a,b}
Mean (SD) BMI (kg/m2)	25.7 (3.3)	25.5 (4.6) ^{b}	25.5 (4.5) ^{a,b}
Mean (SD) CAG repeat length	43.0 (3.0)	42.5 (2.7) ^{a,b}	43.1 (2.4) ^{a,b}

FEASIBILITY RESULTS

- Recruitment targets were narrowly missed; Cohort: 59/60 (98.3%) RCT: 57/60 (93.5%)
- Retention rates at 12 months were ~ 85% in both groups (Figure 3)
- % data completeness for outcomes at baseline ranged from 42.3-100% and at 12 month follow up from 19.2-85.2% (Table 2)

Figure 3: PACE-HD CONSORT flow chart

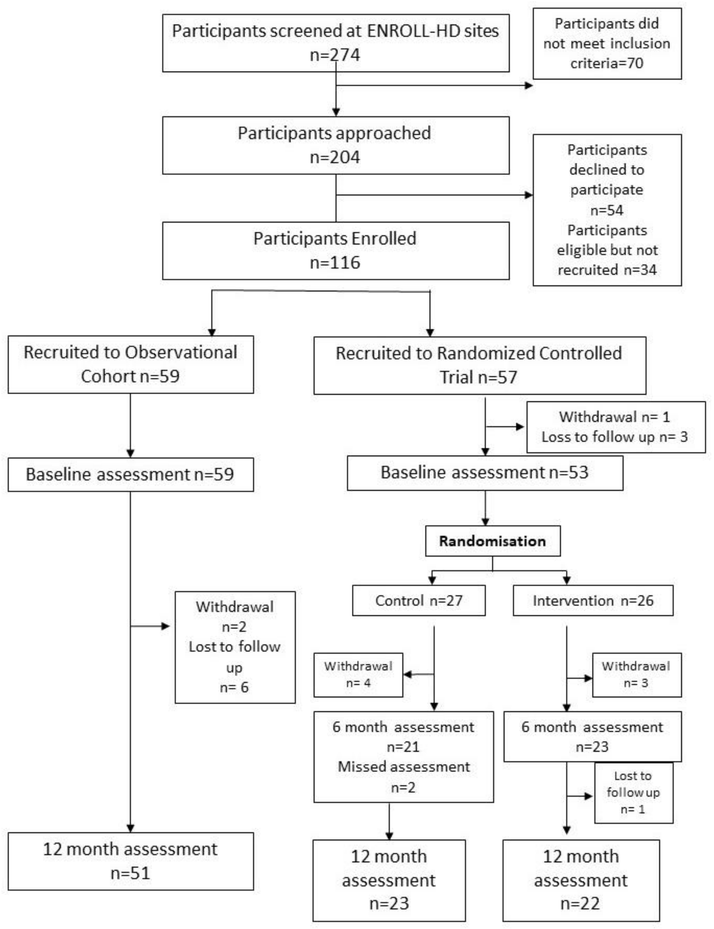
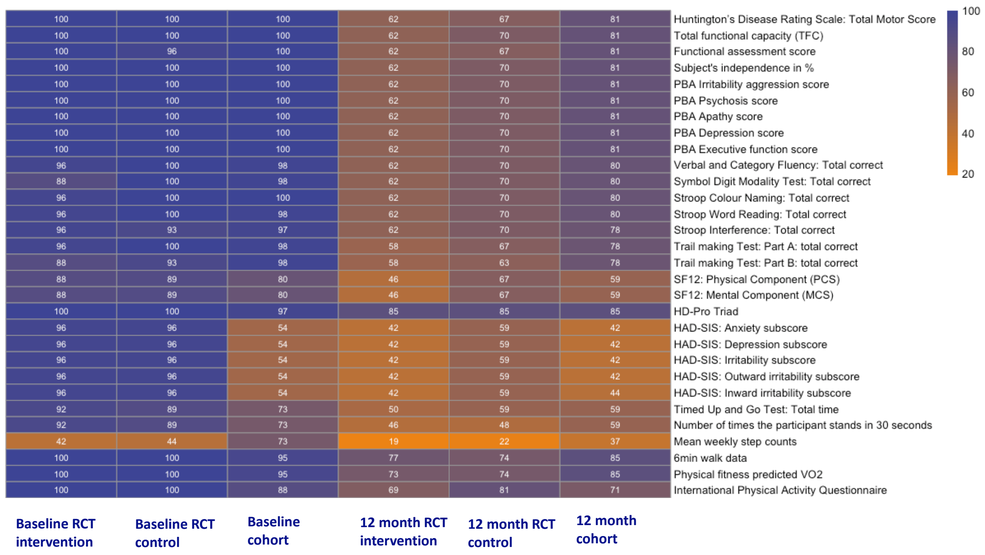


Table 2: Data completeness in the RCT and cohort



PROPENSITY SCORE ANALYSES

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, likely due to small sample sizes (Table 3).

Table 3: Mean [95% CI] of difference for adjusted and unadjusted models and weighting algorithms

Model	*Cohort-Intervention (unadjusted)*	*Observation-Intervention (adjusted)*	*Control-Intervention*	*Weighting Algorithm*	*Max KS*
VO2max_12m ~ treat + cUHDRS + 6' Walk + VO2max	178.31[11.86 , 344.77]	145.38 [-11.02 , 301.77]	38.19 [-140.2 , 216.59]	GBM KS	0.20
cUHDRS_12m ~ treat + cUHDRS + 6' Walk + VO2max	0.58 [-0.16 , 1.33]	0.60 [-0.16 , 1.36]	-0.052 [-0.74 , 0.64]	CBPS	0.20

- There was a promising positive intervention effect on VO2max (mean [95% CI] of difference 145.38 [-11.02 , 301.77] and cUHDRS 0.60 [-0.16 , 1.36] respectively. It was however not possible to achieve adequate balance across any of the groups (indicated when KS values are below 0.1)
- The best performing algorithm between the cohort and intervention and intervention and control groups reported maximum KS values of 0.18/0.19
- A significantly larger sample size would be required to yield a more precise and measurable effect of physical activity on the progression of HD

CONCLUSION

- Recruitment targets were narrowly missed
- Retention at 12 months was excellent
- Pre-specified criteria for the defined minimum dataset collection targets were met
- The TWiC design, with linkage to Enroll-HD, is feasible for long-term physical activity evaluation in HD provided sample size requirements can be achieved

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