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**TITLE:** Physical Activity and Exercise Outcomes in Huntington Disease (PACE-HD): Protocol for a 12-Month Trial Within Cohort Evaluation of a Physical Activity Intervention in People With Huntington Disease

**RUNNING HEAD:** Physical Activity and Exercise Outcomes in HD

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**KEYWORDS:** TWiC, Physical Activity, Huntington Disease, Routine Data, Data Linkage

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**Background.** Exercise is emerging as an important aspect in the management of disease-related symptoms and functional decline in people with Huntington disease (HD). Long-term evaluation of physical activity and exercise participation in HD has yet to be undertaken.

**Objective.** The objective is to investigate the feasibility of a nested randomized controlled trial (RCT) alongside a longitudinal observational study of physical activity and exercise outcomes in people with HD.

**Design.** This will be a 12-month longitudinal observational study (n = 120) with a nested evaluation of a physical activity intervention (n = 30) compared to usual activity (n = 30) using a “Trial within a Cohort” (TWiC) design.

**Setting:** The study will take place in HD specialist clinics in Germany, Spain, and the USA, with intervention delivery in community settings.

**Participants.** The participants will be those with early-mid stage HD participating in the ‘Enroll-HD’ study.

**Intervention.** This will be a 12-month physical activity behavioral change intervention, delivered by physical therapists in 18 sessions, targeting uptake of aerobic exercise and increased physical activity.

**Measurements.** All participants (n = 120) will complete Enroll-HD assessments (motor, cognitive, behavioral, and quality of life) at baseline and 12 months. Additional Physical Activity and Exercise Outcomes in Huntington Disease (PACE-HD) assessments include fitness (predicted VO<sub>2</sub> max), self-reported and quantitative measures of physical activity, disease-specific symptoms, and walking endurance. RCT participants (n = 60) will complete an additional battery of quantitative motor assessments and a 6-month interim assessment. Enroll-HD data will be linked to PACE-HD physical activity and fitness data.

**Limitations.** The limitations include that the embedded RCT is open, and assessors at RCT sites are not blinded to participant allocation.

**Conclusion.** PACE-HD will enable determination of the feasibility of long-term physical activity interventions in people with HD. The novel TWiC design and incorporation of data linkage has potential to reduce participant burden. This design could be applied to other neurological diseases and movement disorders where recruitment and retention are challenging.

## [H2]Background and Rationale

Huntington Disease (HD) is an inherited neurodegenerative disease resulting in the loss of striatal neurons leading to disruption of cortico-striatal pathways. HD is characterised by progressive deficits in cognition, behaviour and movement<sup>1</sup> leading to decline in function, performance of living daily activities and quality of life,<sup>2</sup> with associated caregiver and socioeconomic burdens.<sup>3,4</sup> There is evidence that modifiable lifestyle factors such as education, activity levels and specific motor training may minimize the functional impact of the disease and targeting motor impairments may play a role in delaying disease progression.<sup>5,6</sup>

Clinical studies of short-term exercise interventions have demonstrated improvements in fitness, motor impairment and quality of life in people with HD.<sup>7-12</sup> Longer term pragmatic evaluations of well-defined exercise interventions are required, although such studies are challenging to set up and deliver, particularly in rare diseases. Such studies are limited by poor recruitment, retention and generalizability. Embedded studies, or trials within cohorts (TWiCs),<sup>13</sup> provide an efficient method for recruitment, and may reduce burden through the use of routinely collected prospective outcome data. Generalizability can

be better achieved through access to cohort natural history data, information on routine care as well as relevant lifestyle factors. TWiC 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 physical activity and utilizing quantitative motor and cognitive assessments, is therefore crucial.

## **[H2]Trial Design**

PACE-HD uses a TWiC design,<sup>13</sup> where we are conducting a 12-month, observational cohort study in people with early and mid-stage HD (n = 120) with a nested randomised controlled trial (RCT) of a 12 month physical activity intervention (n = 30) compared to the pragmatic choice of activity as usual (n = 30) (Fig. 1). The intervention will be delivered by physical therapists, targeting uptake of aerobic exercise and increased physical activity. PACE-HD will utilise Enroll-HD,<sup>14</sup> a global clinical research platform designed to facilitate clinical research in Huntington's disease. Core data sets are collected annually on all research participants as part of this multi-centre longitudinal observational study of HD. Data are monitored for quality and accuracy using a risk-based monitoring approach. All sites are required to obtain and maintain local ethics committee approvals. Researchers can apply for access to anonymised Enroll-HD data via a specific data request<sup>15</sup> subject to approval from the Enroll-HD Scientific Review Committee. PACE-HD study data will be supplemented by linking data from participant's annual Enroll-HD assessments. At the conclusion of the study the fully integrated data set will be shared with Enroll-HD and made available to other researchers.

## **[H2]Study Objectives and Outcomes**

The primary objective of this study is to establish the feasibility of a within-cohort nested RCT of a 12-month physical activity intervention in people with HD. The primary outcome is feasibility of the nested RCT in terms of recruitment, retention, data completeness, adherence, fidelity and acceptability. Secondary objectives include: (1) exploration of effect estimates for long-term exercise in HD compared to usual activity, (2) exploration of the influence of physical activity and function on cognitive, motor and functional abilities over a one-year period, and (3) exploration of the predictive validity of physical fitness at 6 months on motor and cognitive outcomes.

## **[H1]METHODS**

### **[H2]Study Population**

Participants (n = 120) will be recruited at six sites. Three sites will serve as observational sites only, and three additional sites will conduct the nested RCT (see supplementary information for full sites details). Sites have been selected as currently recruiting Enroll-HD centres with capability and potential participant capacity required to deliver the study as intended. Potentially eligible participants will be identified according to study inclusion criteria from local Enroll-HD records. Inclusion criteria are: (1) confirmed genetic diagnosis of HD, (2) over 18 years of age, (3) currently registered as a participant in Enroll-HD, and (4) up to and including stage 2 disease status (defined as having a total functional capacity of 7-13). Exclusion criteria are: (1) diagnosis of juvenile onset HD, (2) history of co-morbid neurological conditions such as multiple sclerosis or stroke, (3) an acute orthopaedic condition, eg, a sprained ankle or fracture, and (4) inability or unwillingness to give written informed consent. Interested participants will be provided with written information about the

study and invited to attend a baseline assessment. Written informed consent will be obtained by appropriately trained and delegated site staff.

## **[H2]Sample Size**

As the primary outcome of PACE-HD is feasibility of the nested RCT (in terms of recruitment, retention, data completeness, safety, fidelity and acceptability) a formal sample size calculation for efficacy has not been performed and formal hypothesis testing will not be carried out. Effect sizes and 95% confidence intervals will be presented to inform planning of future studies. For a total sample size of 120 participants recruited into the study we can determine a 95% confidence interval for a 70% retention rate to within  $\pm 8.2\%$ .

## **[H2]Assessments and Secondary Outcome Measures**

All study participants will complete the extended battery of 'Enroll-HD' assessments (eAppendix A)<sup>16</sup> at baseline and 12 months at the participating site (typically hospital or rehabilitation centre). Participants in the nested RCT will complete an additional battery of novel, quantitative motor assessments (Clinch Token Transfer Test (C3T),<sup>17</sup> Geneactiv accelerometers<sup>18</sup> for physical activity monitoring and Q-Motor and Q-Cog assessments),<sup>19</sup> as well as a 6-month interim assessment (Table). Both baseline and 12-month assessments must be conducted within +/- 6 weeks of the participant's annual Enroll-HD visit.

## **[H2]Randomization and Blinding**

At RCT sites, on completion of baseline assessments, participants will be randomly assigned 1:1 to receive the 12-month activity intervention or activity as usual. Randomisation will be performed via the web-based study database using a minimization technique to maintain allocation concealment. The randomization allows for balancing by age (above or below 50 years of age), gender and motor impairment (above or below a Unified Huntington's Disease Rating score (UHDRS) [total motor score] of 40) at baseline and stratified by country. For



pragmatic reasons (including the nature of the intervention) neither participants nor assessors will be blind to allocation.

## **[H2]Physical Activity Intervention**

The PACE-HD intervention is a physical activity behavioural change intervention based on knowledge developed in two previous studies: Exert-HD<sup>9</sup> and Engage-HD.<sup>20</sup> The intervention will be delivered by trained, licensed physical therapists focusing on promoting strategies to engage in aerobic exercise and physical activity (Fig. 2). The program uses a disease-specific workbook and participant-coach interaction that emphasizes relatedness, and promotes participant autonomy and competence.<sup>21</sup> The intervention framework is underpinned by self-determination theory<sup>22</sup> a fundamental component of which is collaborative regulation that specifically considers social–contextual-disease specific conditions. This emphasizes the importance of working in a collaborative way with participants, as well as understanding the progressive nature of HD and the changing needs of the participant so that aspects such as access to healthcare and fitness facilities, social situation and adaptation to a participant’s ongoing cognitive and behavioural status are all taken into account during intervention delivery.

The program will consist of 18 face-to-face, 1:1 physical therapy sessions over 12 months. The timing and location (at participant’s home or rehabilitation facilities at site) of these sessions will be determined by the participant in consultation with their therapist. The suggested timing of interventions sessions are three sessions in month one and two, two sessions in months three and six and monthly sessions in months four, five and 7 to 12. A therapist manual will be used to provide a structured approach to sessions, focusing on exercise uptake (specifically aerobic and strengthening exercises) and engagement in regular physical activity. In partnership with the therapist, participants will develop activity goals that

will be monitored and adjusted throughout. The therapist will work with the participant, using the agreed activity goals as a focus to tailor their exercise program to build up to regular 30 minute periods of exercise 3 to 5 times per week and strengthening exercises 2 to 3 times per week. Participants will be asked to keep monthly physical activity diaries (in paper format or directly entered into the study database) to record the amount and type of physical activity undertaken. Participants will be given the option to use wearable activity monitors (Fitbit Charge 2) to be used throughout the 12-month period as a means to facilitate/monitor activity and sedentary behaviours. We anticipate that some participants will choose not to use a FitBit and so the activity diaries will form the principal method of monitoring exercise. We are not using the FitBit devices as an outcome assessment, but measures elicited from FitBit use will be explored as part of the overall feasibility assessment. Therapists will send regular reminders for attending upcoming appointments, completing exercise diaries and uploading of FitBit data via app-syncing. Preferred communication methods will be discussed at the first session, and can be by phone, e-mail or text messaging.

People with HD need flexibility in terms of access to exercise facilities,<sup>23</sup> and this is critical to successful adherence to exercise in this population. Therefore, each participant will be provided with a choice of exercise equipment options to be used for independent sessions in the home, or participants can choose to exercise in a gym setting.

Participants allocated to activity as usual will not receive the physical activity intervention and will be asked to continue with their usual level of physical activity for the 12 month follow-up period. When participants are randomized to activity as usual they will be referred to the Huntington's Disease Society of America web pages for advice on healthy eating (<http://hdsa.org/living-with-hd/nutrition>). They will not receive visits but will be asked to record their activity in monthly diaries. These participants will also receive monthly prompts via their preferred method of communication to remind them to complete and return

the diaries to their local site. The intervention is fully described in the Template for Intervention Description and Replication (TiDiER)<sup>24</sup> format (eAppendix B).

## **[H2]Data Collection, Management, and Linkage**

All participants will be assigned a unique participant identification number (PID), which is used to identify all data relating to that participant and ensuring confidentiality. Data for all PACE-HD assessments will be entered in real-time into a custom-built database accessed via a secure web interface, after which it is automatically stored in a structured query language (SQL) database. The database is engineered with in-built validations and warning messages that are rigorously tested for the use to ensure data quality.

The C3T assessment will be completed via a native android application on a tablet. On test completion, data is transferred to the C3T SQL Live server and PACE-HD SQL live server simultaneously. Data from Geneactiv monitors will be transferred to the co-ordinating centre where a pre-programmed algorithm will be applied to derive variables for analysis. Variables will be uploaded into the study database.

Participants randomised to the intervention who choose to use Fitbit monitors will be assigned a unique username and password for their devices, and will be asked to sync their devices regularly (approximately every 5 days). We will utilize a backend service platform, FitaBase, to aggregate participant Fitbit data, and at the completion of the study will export summary activity into the study database. Additional clinical data will be obtained from Enroll-HD via a Specific Data Request detailing all the required variables from the extended battery data set. Enroll-HD data exports will be identified using the PACE-HD PID and the HDID (Enroll-HD participant identifier) will not be shared. All sites will maintain PID /HDID linking information. Data exports will be obtained at three time points: after

recruitment of 5 participants per site, at the close of recruitment when all baseline data has been completed, and at the completion of all follow up visits. No follow-up data will be collected from participants that have made a decision to withdraw from the study.

## **[H2]Monitoring**

Data will be monitored remotely for completeness and validity throughout recruitment and follow-up via the study database. A log of all data queries and their resolution will be maintained. Safety events will be monitored by site staff at each interaction with participants. Trial progress in regard to screening, recruitment, retention, non-compliances and safety events will be monitored on a monthly basis at Trial Management Group (TMG) meetings and by the independent Trial Steering Committee (TSC) meeting every six months. This is a low risk study therefore no formal data monitoring committee will be convened. On-site monitoring will be performed by Enroll-HD data monitors for the dual purposes of verifying validity of consent and accuracy of the PID/HDID linking documentation. Participant allocation will be monitored for balance when approximately half the RCT participants have been randomized.

## **[H2]Intervention Fidelity Monitoring**

Fidelity of the intervention will be measured using a combination of therapist self-report checklists (indicating whether the content of each of the sessions was consistent with that specified in the protocol and training manual) and therapist self-assessment completed using a purpose-developed rating scale.<sup>25</sup> Intervention adherence will be assessed as part of the fidelity assessment in the process evaluation.

## [H2]Analysis

Descriptive statistics will summarize key demographic characteristics of all participants in the study (n = 120). Summary data for recruitment, retention and data completeness will be tabulated for the cohort and nested RCT. Adherence rates, safety and fidelity will be summarised for the RCT. The primary feasibility outcome is the proportion of randomized participants that were followed-up at 12 months and will be presented with 95% confidence intervals along with all other feasibility outcomes. Secondary efficacy outcomes from the RCT will be explored and presented with effect sizes and 95% confidence intervals.

Comparability of the observation only (n = 60) and RCT (n = 60) participants at baseline, will be explored using Enroll-HD data. Drop-out bias for the RCT will be assessed by comparing baseline data for those who were followed-up and those who were not at 12 months. No statistical tests will be performed on these data and only appropriate summary data tabulated. For the analysis of secondary outcomes, we will examine the differences in mean scores between arms at 12 months' post-randomization with 95% confidence intervals. Linear models will be used for continuous outcomes where the distributional assumptions of the methods have been met and logistic regression for dichotomous outcomes with results presented as odds ratios and 95% confidence intervals. Covariates in the models will include individual participant characteristics used to balance the randomisation (age, gender, UHDRS total motor score) and the baseline score for each respective outcome. Analysis will be intention to treat and complete case.

A mediation analysis will be performed on VO<sub>2</sub> max recorded at 6 months to assess the role of physical activity and fitness on cognitive, motor and functional abilities. A

sensitivity analysis may be conducted using a mixed model to explore the extent of clustering in potential primary outcome variables by country if numbers permit.

Progression criteria to proceed to further evaluation will be based on the following; over 60% drop-out from the RCT at 12 months will mean no progression, between 40 and 60 % drop-out will mean that changes to the intervention and/or follow-up procedures will be required and less than 30% drop-out at 12 months will indicate that the intervention is suitable for further evaluation without modification.

Summary data of weekly number of steps, average intensity and total intensity of exercise, hours of sleep, average heart rate and peak heart rate as gathered from FitBit activity monitors (intervention group only) will be explored for association with fitness ( $VO_2$  max) at 6 and 12 months. We will also explore data on usual activity from self-reported physical activity assessments in relation to blinded Geneactiv activity data.

Principal Component Analysis will be used to explore the validity of a composite outcome for HD. Recently it has been proposed that a composite outcome has greater validity in detecting disease modification in HD than through the selection of a single primary outcome measure.<sup>26</sup> Where it is hypothesized that exercise interventions will impact of the triad of HD symptoms (motor, cognitive, and behavioral), a composite outcome would be more sensitive in detecting any meaningful disease modification, thus making this exploratory analysis of importance for interventions such as those being studied here. The composite will be based on motor and cognitive outcomes as suggested by Schobel et al<sup>26</sup> and will be compared between arms using confidence intervals.

We will also use propensity score weights to create a pseudo-randomized trial of the intervention that compares the individuals in the intervention arm of the RCT to individuals in our Enroll-HD reference cohort. The propensity score weights will aim to make the two

groups comparable on a range of important characteristics that are associated with HD progression. The treatment effect estimates from the propensity score matched pseudo-randomised groups will be compared with the treatment effect estimate from the randomised groups as a way to assess the utility of propensity score methodology relative to RCTs for obtaining treatment effect estimates for exercise interventions.

## **[H2]Role of Funding Source**

This study has been funded by the Jacques and Gloria Gossweiler Foundation. The funder plays no role in the design or conduct of this study.

## **[H1]ETHICS AND GOVERNANCE**

PACE-HD is sponsored by Cardiff University ([resgov@cardiff.ac.uk](mailto:resgov@cardiff.ac.uk)) and retains overall responsibility for the trial, which is currently recruiting (opened February 2018). Approval for the study has been obtained from the local Institutional Review Board (IRB) at each of the six sites (see supplementary materials for details of each site and their IRBs).

The protocol was written according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement<sup>27</sup> and this manuscript is based upon version 2.0 (23 November 2017) of the study protocol. All protocol amendments will be communicated to participating sites and regulatory authorities by the co-ordinating centre. Study results will be published on ClinicalTrials.gov and in peer-reviewed literature<sup>28</sup>.

## **[H1]DISCUSSION**

This trial incorporates several novel aspects that could transform how we approach the evaluation of long-term exercise interventions in participants with neurodegenerative diseases. HD is an excellent paradigm for other neurodegenerative disease and movement

disorder research. HD is a well- characterized, single gene disorder, as opposed to a cluster of symptomatically aligned disorders with differing aetiologies. This allows research methodologies and therapeutic interventions to be developed and evaluated, which may have high applicability to other related diseases.

This study utilizes a TWiC design with the first longitudinal evaluation of a well-defined exercise intervention in people with HD linking to a global cohort study supplemented with specific exercise-related outcome measures. PACE-HD employs a number of innovative methods for assessing life-style factors across a large, heterogeneous cohort. Incorporating routine data (from Enroll-HD) allows the use of a large, clinically relevant data set without the need for additional tests thereby reducing participant burden. This is particularly important in a rare disease population who are likely asked to be involved in multiple research studies. Wearable technologies are being employed to provide objective measures of physical activity. In combination with prospective activity and clinical data collection, this allows further validation of reliable and sensitive tools for assessing physical activity in real-world settings. Propensity score matching allows for the suitability of pseudo-randomised study designs to be assessed which may be of value in rare conditions where implementing randomised studies is difficult or unfeasible. The innovative systematic approach proposed for this study will have wide-reaching impact that will advance the development of new therapeutic options. It will deliver a realistic, clinically applicable therapeutic option for people with HD that can be implemented in a variety of healthcare settings and can be used as a methodological model for evaluating similar lifestyle interventions in other disease populations.



## **Author Contributions and Acknowledgements**

Concept/idea/research design: C.J.G. Drew, L. Quinn, K. Hamana, R. Playle, B.A. Griffin, M. Kelson, R. Reilmann, A. Rosser, M. Busse

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Fund procurement: C.J.G. Drew, L. Quinn, R. Reilmann, A. Rosser, M. Busse

Providing participants: R. Reilmann

Providing institutional liaisons: L. Quinn, R. Reilmann, A. Rosser, M. Busse

Consultation (including review of manuscript before submitting): K. Hamana, P.

Dimitropoulou, B.A. Griffin, R. Schubert, R. Reilmann, A. Rosser, M. Busse

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## **Ethics Approval**

PACE-HD is sponsored by Cardiff University ([resgov@cardiff.ac.uk](mailto:resgov@cardiff.ac.uk)) and retains overall responsibility for the trial, which is currently recruiting (opened February 2018). Approval for the study has been obtained from the local Institutional Review Board (IRB) at each of the 6 sites (see supplementary materials for details of each site and their IRBs). Written informed consent will be obtained by appropriately trained and delegated site staff.

## **Funding**

PACE-HD is funded by the Jacques and Gloria Gossweiler Foundation.

Enroll-HD is sponsored by Cure Huntington's Disease Initiative (CHDI) Foundation, a nonprofit biomedical research organization exclusively dedicated to developing therapeutics for HD.

### **Clinical Trial Registration**

This trial has been prospectively registered at ClinicalTrials.gov (NCT03344601).

### **Disclosure and Presentations:**

The authors completed the ICJME Form for Disclosure of Potential Conflicts of Interest and reported no conflicts of interest.

PACE-HD was presented at the European Huntington's Disease Network bi-annual plenary meeting in September 2018 in Vienna, Austria, and at a meeting of Enroll-HD centres in Quebec, Canada, in May 2018.

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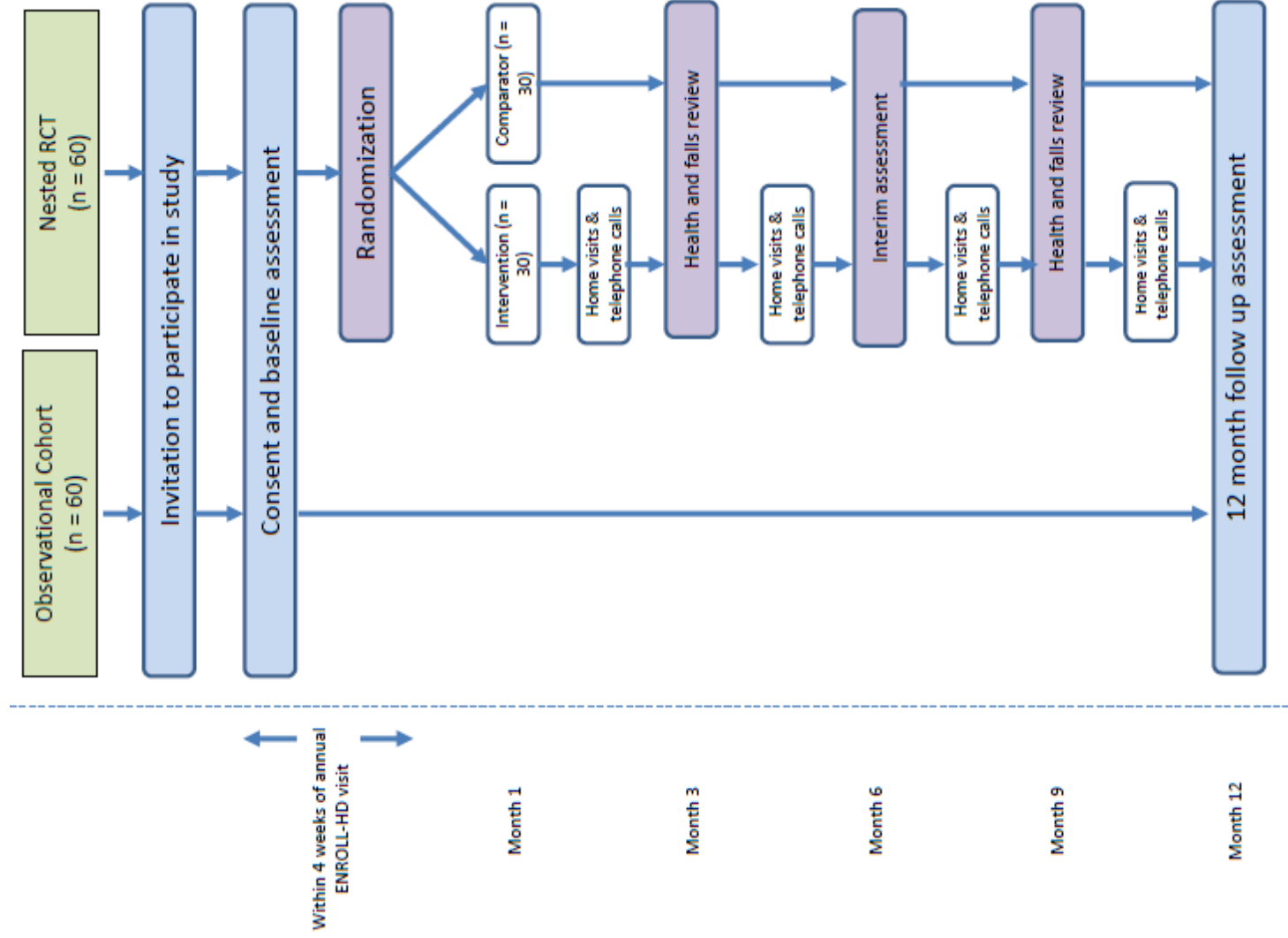
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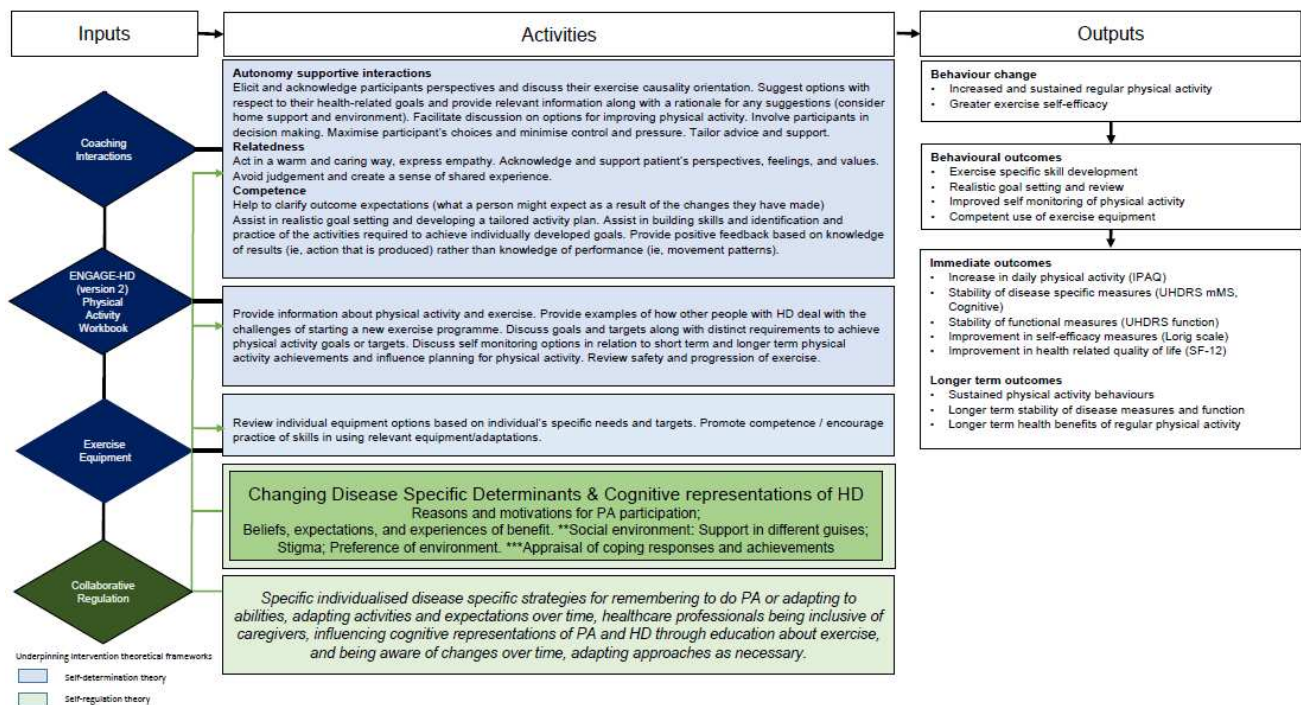
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**Figure 1.** Schematic of participant flow through the study.



**Figure 2.** Logic Model for the PACE-HD intervention. HD = Huntington's disease; IPAQ = International Physical Activity Questionnaire; PA = **Physical Activity**; SF-12 = **12 item quality of life short form survey**; UHDRS = Unified Huntington's disease Rating score; UHDRS mMS = Unified Huntington's disease Rating score (modified Motor Score)



**Table. PACE-HD Specific Assessments<sup>a</sup>**

Construct	Measure	Time Point (month)		
		0	6	12
<b>All Sites</b>				
<b>Fitness</b>	Predicted VO <sub>2</sub> Max will be measured during stepwise incremental exercise test. <sup>29</sup> The test is performed on a cycle ergometer with participants seated in a standardized position. Participants will attempt to maintain a cadence of 50 revolutions per minute (rpm), starting at 50 Watts and increasing by 25 Watts every 2 minutes until test termination. The test will be terminated when the participant reaches volitional exhaustion or cadence drops by 10 rpm. At the end of each minute, work-rate (Watts), rating of perceived exertion (Borg RPE scale), and heart rate will be recorded for analysis and conversion to predicted VO <sub>2</sub> max score.	✓	✓ (RCT only)	✓
<b>Walking endurance</b>	The 6-minute walk test will be used as a measure of walking endurance. This test evaluates the distance walked over a 6 minute period, and has been validated for use in HD. <sup>30</sup>	✓	✓ (RCT only)	✓
<b>Participant-reported clinical symptoms</b>	HD Pro-Triad, <sup>31</sup> a quality of life measure specific to HD, will be used to assess disease specific symptoms including cognitive decline, emotional/ behavioral disturbance, and motor dysfunction.	✓		✓
<b>Physical activity monitoring</b>	Brunel Lifestyle Physical Activity Questionnaire <sup>32</sup> is a validated self-report instrument that measures the planned and unplanned dimensions of lifestyle physical activity.	✓		
	Geneactiv accelerometers <sup>18</sup> are research grade wrist-worn devices that continuously record physical and sedentary behaviours without feedback provided to the wearer. <sup>33</sup> We are developing algorithms specific to HD to transform the accelerometer data into summary data specifying periods of physical activity, sedentary, and sleep behaviours. <sup>34</sup> Participants will be given the monitors at baseline assessment and will be asked to return them after 7 days' wear. Wear time will be 24 hours a day, except when showering. For validation of sleep time compared to sedentary time, participants will be asked to complete and return sleep diaries for the 7-day period of physical activity assessment.	✓	✓ (RCT only)	✓
	International Physical Activity Questionnaire (IPAQ, Short Form) measures the intensity and duration of physical activity undertaken in the last 7 days. It will be used to assess 7-day physical activity and to validate outputs of the physical activity monitors. <sup>35</sup>	✓	✓ (RCT only)	✓
<b>RCT Sites Only</b>				

<b>Motor and dual task function</b>	The Clinch Token Transfer Test (C3T) <sup>17</sup> is a novel dual-task assessment of bilateral, upper motor function that consists of 3-coin transfer tasks which increase in difficulty (baseline simple, baseline complex, and a dual task). The time taken to pick up and transfer the coins from dominant to non-dominant hand and place into a purpose developed box is recorded. The addition of cognitive load increases the task complexity. This has been shown to be highly sensitive across all stages of HD.	✓	✓	
<b>Motor function</b>	Q-Motor was developed in TRACK-HD and TRACK-ON-HD where motor tasks are related to functionally relevant everyday tasks. All Q-Motor assessments are conducted using pre-calibrated and temperature controlled force transducers and 3D motion tracking <sup>19</sup> sensors with very high sensitivity and test-retest reliability across sessions and sites in a multicenter clinical trials involving participants with HD. <sup>36,37</sup>	✓		✓
<b>Cognitive function</b>	Q-Cog assessments deploy the technology used in the Q-Motor system to benefit from the high accuracy of the sensors in tasks with high cognitive load with the goal of providing a sensitive quantitative assessment of cognitive deficits in HD. Q-Cog assessments have high discriminative ability. <sup>38</sup> Longitudinal performance has not yet been evaluated.	✓		✓
<b>Self-efficacy</b>	The Lorig Self Efficacy <sup>39</sup> scale is a 6 item questionnaire validated for the assessment of self-efficacy in people with chronic conditions. In this study, it will be utilized to measure self-efficacy related to exercise (exercise sub-scale only)	✓	✓	✓

<sup>a</sup>HD = Huntington disease; rct = randomized controlled trial; TRACK-HD = A 3 year

prospective, observational study of people with HD and controls where imaging, cognitive and motor assessment data was collected. TRACK-ON-HD = extension of TRACK-HD to include pre-manifest HD participants