Centre for Trials Research
Canolfan Ymchwil Treialon

Gossweiler Foundation

UKCRC Registered Clinical Trials Units

PACE-HD

PHYSICAL ACTIVITY AND EXERCISE OUTCOMES IN HUNTINGTON'S DISEASE (PACE-HD)

A longitudinal cohort study with nested randomised pragmatic controlled trial to evaluate physical activity and exercise related outcomes in people with Huntington's disease.

PROTOCOL VERSION 3.0 13/11/18

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SIGNATURE PAGE

The undersigned confirm that the following protocol has been agreed and accepted and that the Chief Investigator agrees to conduct the trial in compliance with the approved protocol and will adhere to the principles outlined in the relevant trial regulations, GCP guidelines, and Sponsor's SOPs.

I agree to ensure that the confidential information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor. I also confirm that I will make the findings of the trial publically available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as planned in this protocol will be explained.

Director:	Prof Monica Busse	
		30/11/18
Name	**Signature**	**Date**
Co-Chief Investigators:	Dr Lori Quinn/ Prof Monica Busse	
		30/11/18
Name	**Signature**	**Date**

General Information This protocol describes the PACE-HD study and nested randomised trial and provides information about the procedures for entering participants into the study. For the purposes of consistency in this document, we use the term trial when referring to any component of the PACE-HD cohort or nested RCT. The protocol should not be used as a guide, or as an aide-memoire for the treatment of other participants. Every care has been taken in drafting this protocol; however, corrections or amendments may be necessary. These will be circulated to the known Investigators in the trial. Problems relating to the trial should be referred, in the first instance, to CTR.

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Trial Co-ordination:

The PACE-HD trial is being coordinated by the Cardiff University Centre for Trials Research (CTR). This protocol has been developed by the PACE-HD Trial Management Group (TMG).

For **all queries** please contact the PACE-HD team through the main trial email address. Any clinical queries will be directed through the Trial Manager to either the Chief Investigator or a relevant Co-Investigator.

Main Trial Email:	PACEHDtrial@cardiff.ac.uk	
Trial Administrator:	Barry Lloyd	Tel: 029 2068 8611
Trial Manager:	Dr Cheney Drew	Email: DrewC5@Cardiff.ac.uk
Data Manager:	Rhys Williams-Thomas	
Trial Statisticians:	Dr Rebecca Playle Dr Katie Taiyari	
Director:	Prof. Monica Busse	

Randomisations:

Randomisation
To randomise a participant, you will need to use your allocated log in to access the PACE-HD database and navigate to 'new participant' (See section 16.1.1 for web address).

Clinical queries:

Clinical queries
PACEHDtrial@cardiff.ac.uk
All clinical queries will be directed to the most appropriate clinical person.

Serious Adverse Events:

SAE reporting
Where the adverse event meets one of the serious categories, an SAE form should be completed in the trial database (https://pacehd.sewtudb.cf.ac.uk/login/) or by completing a paper SAE form and e-mailing to PACEHDTrial@cardiff.ac.uk by the responsible clinician within 24 hours of becoming aware of the event (See section 13 for more details).

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Glossary of abbreviations

AE	Adverse Event
AR	Adverse Reaction
C3T	Clinch Token Transfer Test
CF	Consent Form
CI	Chief Investigator
CRF	Case Report Form
CTR	Centre for Trials Research
CTU	Clinical Trials Unit
CU	Cardiff University
GCP	Good Clinical Practice
GP	General Practitioner
HD	Huntington's Disease
HDID	HD Identification Number
IC	Informed consent
ICH	International Conference on Harmonization
IRB	Institutional Review Board
ISF	Investigator Site File
PI	Principal Investigator
PID	Participant Identification Number
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality control
QL (QoL)	Quality of Life
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SOP	Standard Operating Procedure
TFC	Total Functional Capacity
TMF	Trial Master File
TMG	Trial Management Group
TSC	Trial Steering Committee

1 Amendment History

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment No. *(specify substantial/non-substantial)*	**Protocol version no.**	**Date issued**	**Summary of changes made since previous version**
1	2.0	03/05/2018	1) Addition of patient reported sleep diaries as part of the week long physical activity assessment at baseline and 12 month follow up assessments. 2) Removal of work productivity questionnaire from list of linked Enroll-HD data 3) Alteration of 'intervention compliance' to ' intervention adherence' and additional explanatory information inserted 4) Correction of randomisation stratification
2	3.0	13/11/2018	1) Change to recruitment timelines in section 6 2) Addition of detail on the requirement for therapists to complete self-assessment checklists in section 11.2 3) Addition of SWAT regarding the completion of activity diaries in section 12. 4) Changes to trial staff

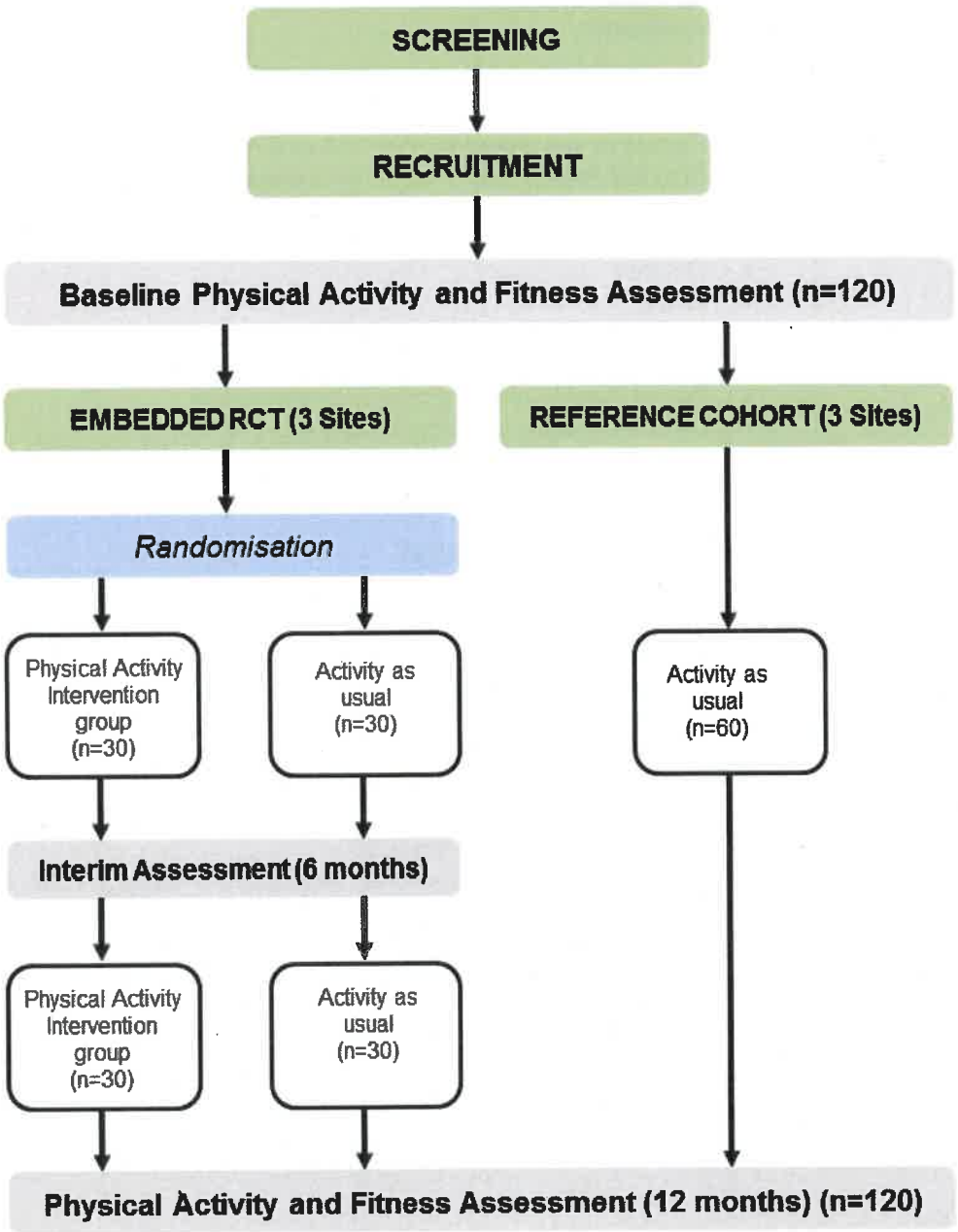
2 Synopsis

Short title	**P**hysical **AC**tivity and **E**xercise Outcomes in Huntington's Disease
Acronym	PACE-HD
Clinical phase	Phase II
Funder and ref.	Jacques and Gloria Gossweiler Foundation
Trial design	Observational cohort study with nested randomised trial of long term exercise compared to usual physical activity
Trial participants	People with a confirmed genetic diagnosis of Huntington's Disease.
Planned sample size	120
Inclusion criteria	• Diagnosis of HD, confirmed by genetic testing • Above the age of 18 • A current participant on the Enroll-HD study (a worldwide observational study of HD families, which provides a platform for clinical studies) • Up to and including stage 2 disease status (TFC 7-13)
Exclusion criteria	• Diagnosis of juvenile onset HD • History of co-morbid neurological conditions such as multiple sclerosis or stroke • Acute (within 1 month) orthopaedic conditions e.g. ankle sprain or fracture • Inability or unwillingness of participant or legal guardian to give written informed consent
Intervention duration	Nested RCT: 12 months
Follow-up duration	Observational Study: 12 months Nested RCT: 12 months
Planned trial period	24 months
Primary objective	1. To establish feasibility of a within cohort nested randomised trial of a 12 month physical activity intervention in people with HD
Secondary objectives	1. To explore effect estimates for long term (12 months) exercise in HD compared to usual activity. 2. To explore the influence of physical activity and physical function on cognitive, motor and functional abilities over a one-year period. 3. To explore the predictive validity of physical fitness at 6 months on

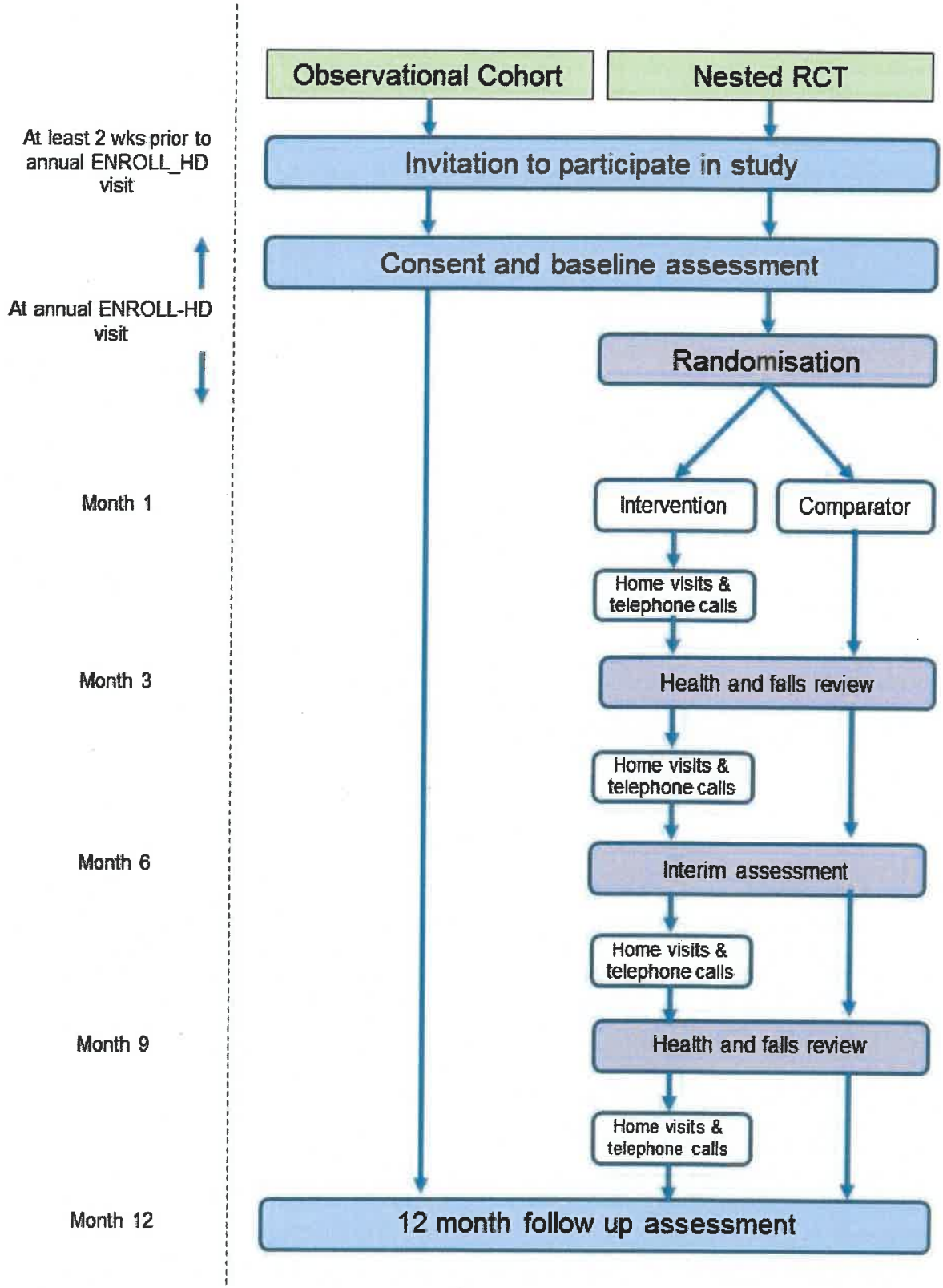
	motor and cognitive outcomes.
Primary outcomes	Feasibility (data completeness, recruitment, retention, safety, adherence, fidelity, acceptability)
Secondary outcomes	Trial data: • Fitness as measured by VO_2 max at 6-month • Physical Activity over 7 days (as measured by Geneactiv accelerometers) • Walking endurance as measured by the 6-minute walk test • Q-motor • Q cog • Upper limb dexterity (Clinch Token Transfer Test) • International Physical Activity Questionnaire (IPAQ) • Brunel lifestyle physical activity questionnaire • Disease-specific symptoms (HD-PRO-TRIAD) • Self-Efficacy (Lorig Self-Efficacy Scale) Linked Enroll-HD data (12 months): • Huntington's Disease Rating Scale Total Motor Score • Symbol Digit Modality Test • Stroop Word Reading • Stroop Colour Naming • Stroop Interference • Verbal and Category Fluency • Self-reported quality of life (SF-12), • Anxiety, depression and irritability (Hospital Anxiety and Depression scale-Snaith irritability scale)) • Functional ability (Functional Assessment Scale, Total Functional Capacity and Independence scale) • Health Service use (Client Service Receipt Inventory) • Timed Up and Go Test • 30 second chair stand test
Intervention	Participants will be individually randomised (1:1) to a 12-month long-term physical activity and coaching intervention, or usual activity. Coaching will focus on strategies to facilitate adherence to exercise.

3 Trial summary & schema

3.1 Trial schema



3.2 Participant Flow



3.3 Trial lay summary

Huntington's disease (HD) is a genetic, degenerative neurological disease that affects individuals in their third to fourth decade of life. Individuals with HD can live 15-20 years with manifest HD, and the complex disease symptoms, including motor, cognitive and behavioural impairments, result in loss of functional independence and progressive escalation of healthcare costs[1]. The personal, social and economic consequences of HD are devastating, especially as there are currently no disease modification therapies available.

Environmental factors, including exercise and physical activity, have the potential to minimize the functional impact of this chronic disease. Animal models of HD have provided the first evidence that exercise has the potential to delay or alter disease progression and a range of studies in HD clinical populations have now shown that short-term exercise (3 months or less) is well tolerated and has the potential to improve quality of life, fitness and motor impairments in HD[2–6]. Despite these promising studies, there are critical knowledge gaps that currently prevent the intelligent application of exercise as a therapeutic intervention in HD. Firstly, there have been no prospective evaluations of the potential role of physical activity and exercise in disease modification in HD. To date, only retrospective data has suggested that lifestyle factors, including sedentary behavior, could negatively affect disease progression in HD. Secondly, we do not know if sustained exercise (> 3 months) is feasible, and if it has the potential to improve cognitive outcomes, such as has been shown in other neurodegenerative diseases[7,8]. Such longer-term studies are also essential to elucidate the potential for exercise to have a disease-modifying effect; the mechanisms through which such improvement may occur have yet to be explored.

In this trial, we will employ a systematic approach for routinely collecting prospective physical activity and fitness data and monitoring physical activity behaviour in 120 individuals with HD. We will use a database to track physical activity and exercise behaviour alongside standardized disease-specific outcome measures during two annual visits. Assessment will incorporate VO2max, a surrogate measure of fitness and a direct measure of oxygen uptake that is related to central nervous system (CNS) function and structure[9,10], and the use of wearable technologies (Gene-activ activity monitors) that capture and quantify dose (frequency, duration, intensity) of physical activity in a large HD cohort. We will further conduct a within-cohort randomized control trial (RCT) of a 12-month exercise intervention in HD, comparing a supported structured aerobic exercise training program to activity as usual. This intervention will also incorporate a physical activity coaching program[11] developed and evaluated by our group with a view to encouraging longer term exercise uptake.

4 Background

Huntington's disease (HD) is a neurodegenerative disease causing dysfunction and death of medium spiny striatal projection neurons and thus disruption of corticostriatal pathways with resultant impairment of cognition, motor function, and behaviour[12]. These impairments result in decreasing independence in activities of daily living and quality of life[13] even from relatively early in the disease. The potential to develop interventions to facilitate independent living and strategies to manage symptoms is crucial to managing both the personal and economic effects of this devastating disease. Although to date there are no successful pharmacological interventions that are able to slow disease progression, there is now clear emerging evidence of disease specific motor function and general health benefits of shorter exercise in HD [2,4,5]. Although we have been able to successfully deliver exercise and behaviour change interventions in HD over the shorter term, we now need studies that actively facilitate exercise adherence over a longer term (e.g. one year) to realistically begin to assess the impact of physical activity and structured exercise on disease progression.

Therapeutic exercise interventions present an exciting, transformative area of research in neurodegenerative diseases.[14,15] Addressing motor impairments in neurodegeneration may provide a long-term beneficial effect in delaying disease progression and maximizing functional abilities over a

longer period. Loss of independent mobility and care dependency have been shown to be important predictors of nursing home admissions[16,17]. The potential to develop interventions that facilitate independent living and strategies to manage symptoms is crucial to managing both the personal and economic effects of this devastating disease. Although to date there are no successful pharmacological or other interventions that are able to slow disease progression, there is some suggestion that lifestyle factors, such as activity level and education alongside specific motor training may help to drive compensatory neural networks, that may in turn compensate for the failing brain, and change the course of the disease.[18–21] Studies to date in HD have relied on retrospective data[19], and robust evaluation of lifestyle factors contributing to disease progression is needed. If shown to be effective, exercise programs have the potential to be used in combination with disease-modifying drugs, cell replacement therapy or genetic manipulations, when available, to maximize the functional benefits of these interventions by facilitating adaptive neuroplasticity.[22,23]

Our group has set out to systematically evaluate the feasibility of exercise and physical activity interventions in people with HD using a two-pronged approach. Our first approach evaluated the feasibility of short-term aerobic and strengthening exercise programs in HD.[5] This led to our recently completed study funded by the Gossweiler Foundation, Exert-HD, a 3-month randomized controlled trial of aerobic (performed between 60-85% age predicted heart rate max) and strengthening exercise. Participants in the exercise group demonstrated significantly improved predicted VO2 max and Unified Huntington Disease Rating Scale (UHDRS) modified Motor Scores (mMS), but no effect was seen on cognition or other measures of motor function.[4] This study had high retention and adherence, and was well tolerated by participants. Alongside this, we developed and evaluated the feasibility of a behavioural change intervention to increase levels of physical activity (*Engage-HD*; ISRCTN65378754).[11,24] The intervention aimed to evaluate the efficacy of a physical activity intervention (6 sessions over 14 weeks) utilizing a workbook-based behavioural change program compared to a social contact control. This study demonstrated improvements in self-reported physical activity, self-efficacy for exercise, and cognition, however no changes were noted for HD-specific motor function.[25]

In PACE-HD we seek to address three issues that naturally arise from the preliminary studies completed to date. **First, there has been no evaluation of long-term (e.g. 12 month) aerobic and strengthening exercise interventions in HD.** While studies to date have demonstrated improvements in motor and cognitive function in the short term, it is unclear whether exercise behaviour can be maintained over a longer term, and to what degree any improvements in cognition or motor function can be maintained or enhanced with a longer term intervention.

Second, there is a lack of understanding of the role of physical activity in disease progression in HD. Our preliminary work has utilized 7 day activity monitors[5] that have improved functionality to obtain more detailed data on physical activity behavior, including light and moderate- vigorous physical activity, sedentary behavior and sleep patterns over the intervention period. In this trial, we will utilize 7 day activity monitors to evaluate activity patterns longitudinally over a year period in a cohort of 120 people with HD. This longitudinal evaluation alongside standardized evaluations of motor, cognitive and functional abilities will aid in validation of wearable activity devices and evaluate how physical fitness and physical activity may be related to disease progression.

Third, there is lack of understanding of the mechanisms by which exercise may achieve its effect in HD. Trials of longer term exercise interventions are difficult to deliver, not least in terms of the complexity of the intervention but also due to the challenges in accurately characterising the different dimensions of real-life physical activity and understanding individual response to exercise. Our preliminary research has shown that exercise has the potential to improve aerobic fitness using measurements of estimated (predicted) VO2max. This trial will incorporate longitudinal assessment of VO2max, a surrogate measure of fitness and a direct measure of oxygen uptake that is related to central nervous system (CNS) function and structure.[9,10]

4.1 Rationale for current trial/Justification of Treatment Options

The research questions for this trial are:

1. What is the feasibility of a within cohort, pragmatic, randomised controlled trial of a 12-month physical activity intervention in people with HD?
2. Does physical fitness and participation in regular physical activity predict cognitive, motor and functional abilities over a one-year period?

This trial includes two components: 1) A 12-month longitudinal evaluation of physical fitness and physical activity assessments in a cohort of individuals with HD (n=120) recruited from the Enroll-HD platform study; and 2) A within cohort (nested) RCT, in which we will conduct a randomised evaluation of a longer-term (12 month) physical activity intervention (n=60). Participants will be recruited from the larger cohort and will be individually randomised (1:1) to a 12-month physical activity and coaching intervention, or usual activity. This coaching will focus on strategies to facilitate adherence to exercise, and will incorporate use of physical activity monitors (FitBits) to aid in goal setting and physical activity monitoring over the course of the intervention. In addition, all participants will receive information (verbal and handouts) about the importance of healthy eating and maintaining weight with HD. This intervention is modelled on our previous studies, which have been feasible and acceptable to people with early-mid stage HD. Those allocated to usual activity and those from the other 3 sites who are not randomised will provide reference data (n=90) from their routine, annual Enroll-HD assessments for evaluation of exercise effects in those who are randomised to the long-term physical activity intervention (n=30).

5 Trial objectives/endpoints and outcome measures

5.1 Primary objectives

1. The primary objective is to establish feasibility of a within cohort nested randomised trial of a 12-month physical activity intervention in people with HD.

5.2 Secondary objectives

1. To explore effect estimates for long term (12 months) physical activity in HD compared to usual activity.
2. To explore the influence of physical activity on cognitive, motor and functional abilities over a one-year period.
3. To explore the predictive validity of physical fitness at 6 months on motor and cognitive outcomes.

5.3 Primary outcomes measure(s)

The primary outcome measures for this trial are focused on feasibility of the 12-month physical activity intervention.

- **Recruitment rate** will be assessed using site recruitment logs.
- **Retention rate** will be measured as the percentage of individuals who completed the intervention.
- **Adherence rates** will be defined as percentage of intervention sessions completed,
- **Safety** will be assessed through monthly documentation completed by therapists administering the intervention, which captures information on falls history, medication

changes, healthcare service use and hospital admissions (classified as serious adverse events).

- **Fidelity** of the interventions will be assessed via review of coach documentation and activity monitor data.
- **Data completeness** will be assessed by the percentage of data entered into the database.

5.4 Secondary outcomes measure(s)

- A range of secondary outcome measures will be collected to explore effect estimates for the RCT as well as explore the role of physical activity and physical fitness on cognitive, motor and functional abilities. The majority of these measures will be collected as part of the core and extended batteries of the Enroll-HD protocol, and include motor function (Unified Huntington Disease Rating Scale Total Motor Score, cognitive battery (Symbol Digit Modality Test, Stroop Word Reading, Stroop Colour Naming and Stroop Interference, Verbal and Category Fluency), functional ability (Functional Assessment Scale, Total functional capacity and independence scale), self-reported quality of life (SF-12), anxiety, depression and irritability (Hospital Anxiety and Depression scale- Snaith irritability scale), service use (Client Service Receipt Inventory), Timed up and go Test and 30 second chair stand test.
- Additional measures to be obtained alongside the Enroll-HD assessments will include: VO_2max as measured by a stepwise incremental exercise test will provide an evaluation of intervention effectiveness; Walking endurance as measured by the 6-minute walk test, functional and cognitive ability as measured by the Clinch Token Transfer Test (C3T), Q-Motor and Q-Cog assessment batteries, physical activity (as measured by the International Physical Activity Questionnaire and Brunel lifestyle physical activity questionnaire and 7 day physical activity monitors (GeneActiv devices)), self-efficacy (Lorig Self-Efficacy Scale) and disease-specific symptoms (HD-PRO-TRIAD).

For specific details on outcomes please go to section 12.1

6 Trial design and setting

This trial is a longitudinal observational study of physical activity and physical fitness in 120 people with early-mid stage HD (assessed as having an overall low risk) with an additional nested evaluation of a 12-month physical activity intervention (n=30) compared to usual activity (n=30).

Participants will be recruited from current Enroll-HD sites in Europe and the USA. Enroll-HD is a worldwide research platform that has as its core a longitudinal observational study of HD families. Enroll-HD provides an infrastructure to support clinical studies such as the one proposed here. Recruitment for the longitudinal study and the nested RCT will be conducted over a period of 15 months, both with a 12 month follow up period. The trial is expected to last a total of 27 months. The end of the trial will be defined as last participant, last visit, which will be the 12-month assessment. This could be a participant in either the observational cohort or nested RCT.

All participants will undergo a baseline assessment as part of their annual Enroll-HD visit where standard measures will be collected as per the Enroll-HD study protocol. Additional assessments pertaining to physical activity will also be performed (see section 12.1 for further details). The additional assessments should be collected ± 4 weeks of the annual ENROLL visit. These assessments will be repeated after 12 months within ± 4 weeks of the next annual Enroll-HD visit. For those participants taking part in the nested RCT, an additional assessment will be performed at 6 months. For participants randomised to receive the physical activity and coaching intervention in the nested RCT, they will receive the intervention over a 12-month period which will include 18 home or site visits (pragmatically scheduled) and additional supportive monthly telephone calls.

All data will be entered directly into the trial database by local researchers via an individual log-in. Where data is obtained from third party sources exports will be obtained on a monthly basis for upload into the trial database.

6.1 Risk assessment

A trial risk assessment has been completed to identify the potential hazards associated with the trial and to assess the likelihood of those hazards occurring and resulting in harm. This risk assessment has been completed in accordance with the MRC/DH/MHRA Joint project guidance document 'Risk-adapted approaches to the management of Clinical Trials of Investigational Medicinal Products' and includes:

- The known and potential risks and benefits to human subjects
- How high the risk is compared to normal standard practice
- How the risk will be minimised/managed

This trial has been categorised as Low (comparable to the risk of standard medical care). A copy of the trial risk assessment may be requested from the Trial Manager. The trial risk assessment is used to determine the intensity and focus of monitoring activity (see section 23.1).

7 Site and Investigator selection

This trial will be carried out at participating Enroll-HD sites in Europe (within the European Economic Area) and the United States. All sites who are interested in participating in the trial will be required to complete a site feasibility questionnaire circulated by the Enroll-HD study team to confirm that they have adequate resources and experience to conduct the trial. Before any site can begin recruitment a Principal Investigator at each site must be identified. The following documents must be in place and copies sent to the PACE-HD Trial email account (see contact details on page 3):

- Confirmation (by letter) of local permission to conduct the research at the site. The nature of this approval will vary according to the country the site is located. Favourable opinion of host care organisation/PI from Main Ethics committee
- A signed Trial Agreement
- Current Curriculum Vitae and GCP training certificate of the Principal Investigator (PI)
- Completed Site Delegation Log and Roles and Responsibilities document
- Full contact details for all host care organisation personnel involved, indicating preferred contact
- A copy of the most recent approved version of the Participant Information Sheet(s) and Consent Form(s) on host care organisation headed paper Returned copy of the Self-Evident Correction Log signed by the PI.

Upon receipt of all the above documents, the Trial Manager will send written confirmation to the Principal Investigator/lead therapist detailing that the centre is now ready to recruit participants into the trial. This letter/email must be filed in each site's Site File. Along with the written confirmation, the site should receive their trial pack holding all the documents required to recruit into the Trial and details regarding how to support participants to obtain relevant exercise equipment. Occasionally during the trial; amendments may be made to the trial documentation listed above. CTR will issue the site with the latest version of the documents as soon as they become available. It is the responsibility of the CTR to ensure that they obtain the necessary local approvals for the new documents.

Site initiation will be by performed remotely via Skype/videoconferencing.

8 Participant selection

Participants are eligible for the trial if they meet all of the following inclusion criteria and none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Trial Manager before registration.

8.1 Inclusion criteria

- Diagnosis of HD, confirmed by genetic testing
- Above the age of 18
- A participant (current or newly enrolled) in the Enroll-HD study
- Up to and including stage 2 disease status (TFC 7-13), but participants must have a diagnostic confidence of 4.

8.2 Exclusion criteria

- Diagnosis of juvenile onset HD
- History of co-morbid neurological conditions such as multiple sclerosis or stroke
- Acute orthopaedic conditions (within a month) e.g. ankle sprain or fracture
- Inability or unwillingness of participant or legal guardian to give written informed consent

9 Recruitment, Screening, Registration and Randomisation

9.1 Participant identification and pre-screening

Participants will be identified from registered Enroll-HD participants at each site. If an individual is deemed suitable for PACE-HD and not yet recruited to Enroll, they could be recruited onto Enroll-HD at that time however must be enrolled on Enroll-HD prior to randomisation. Enroll-HD is a global research platform that has at its core a worldwide observational study for Huntington's disease families(https://www.enroll-hd.org/learn/about-this-study/). Enroll-HD monitors the onset of the disease and its progression in different people and open to the following categories: gene carriers, gene negative and family controls.

One of the optional components within the Enroll-HD study is the request to give permission to be contacted to receive information about other additional and affiliated HD research projects. In consenting to participate in the Enroll-HD study, participants also give their permission for their coded data to be made available to any researchers with a legitimate research project who wants to better understand HD. Only coded clinical data are shared with the researchers therefore, the risk that identifying information will be accidentally disclosed is low.

Participants registered on Enroll-HD at participating sites will be reviewed for eligibility (pre-screening) for inclusion in the trial by Enroll-HD research staff. A list will be generated prior to the start of recruitment of ENROLL-HD participants that satisfy the inclusion criteria at each site. A list of all ENROLL participants and the generated lists of potentially eligible participants will be sent to the PACE-HD trial manager prior to the start of recruitment and will be updated every quarter. The trial manager will use the list of potentially eligible participant to pre-populate screening logs to be sent to individual sites. Sites will be asked to cross reference potentially eligible participants in the screening log with their own records to assess eligibility against the exclusion criteria. Those that fit the inclusion criteria and none of the exclusion criteria will be sent an invitation to participate in the trial by the local research team prior to or at their next Enroll-HD visit, provided that in Enroll-HD the participants have consented to be contacted between trial visits to receive information about HD research studies. All interested potential participants will be given as long as they need to read the material and discuss with their

families and carers before being asked to make any decisions. Participants will have the opportunity to ask any questions they have about the trial and discuss their potential involvement before providing informed consent.

9.2 Screening logs

A log of all potentially eligible participants (as defined by the trial inclusion criteria) at each site will be held. This will be pre-populated by the PACE-HD trial manager with information obtained via the ENROLL-HD co-ordinator (see section 9.1) A record of any potentially eligible participants meeting exclusion criteria and thus deemed ineligible will be recorded in the screening log. The log will contain a record of all those approached to take part in the trial and subsequently declined to participate, were excluded from participation following a screening assessment or were enrolled in the trial. Reasons for not participating will be recorded. When at site, logs may contain identifiable information, but this **must** be redacted prior to being sent to the CTR.

The screening log should be sent to PACEHDtrial@cardiff.ac.uk monthly (see section 19 for further detail on data monitoring/quality assurance).

All pre-screening (conducted as part of the process of participant identification) and screening information will be recorded centrally to inform the trial CONSORT diagram (Appendix I).

9.3 Recruitment rates

A total of 120 participants will be recruited into the prospective observational cohort at 6 sites. Recruitment is expected to take approximately 15 months, with a target of 1-2 participants a month.

9.4 Informed consent

Consent may be taken by qualified researchers or clinicians at each site, details of which will be recorded on the delegation log at the site. Please note, only when written informed consent has been obtained from the participant and they have been randomised/enrolled into the trial can they be considered a trial participant. Participants should always be asked to sign a consent form before conducting any trial mandated procedures. One copy should be given to the participant but the original copy should be kept in the investigator site file.

The right of the subject to refuse to participate in the trial without giving reasons must be respected. After the participant has entered the trial, the investigator must remain free to give alternative treatment to that specified in the protocol, at any stage, if he/she feels it to be in the best interest of the participant. However, the reason for doing so should be recorded and the participant will remain within the trial for the purpose of follow up and data analysis according to the treatment option to which he/she has been allocated. Similarly, the participant must remain free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing his/her further treatment.

9.5 Registration and Randomisation

9.5.1 Registration

Potential participants will be screened for eligibility by local site teams as described in section 9.1. Those meeting eligibility criteria and providing informed consent will be registered as a trial participant and assigned a unique trial identification number prior to baseline data collection. At sites conducting the nested RCT, the participant will then undergo a further safety assessment to determine their ability to take part safely in the interventional trial prior to baseline data collection. Only those passing the safety screening assessment will be eligible for randomisation. The Malnutrition Universal Screening Tool' ('MUST') for adults will be completed at baseline for those in the intervention sites.

9.5.2 Randomisation

The randomisation will be stratified by country. Participants within intervention countries will be randomised in a 1:1 ratio to receive the intervention or continue with their current regime of physical activity. A minimisation technique will be used for randomisation to ensure a similar distribution of selected participant factors between trial groups. The first participant is truly randomly allocated; for each subsequent participant, the treatment allocation that minimises the imbalance on the selected factors between groups at that time is selected. That allocation may then be used, or a choice may be made at random with a heavy weighting in favour of the intervention that would minimise imbalance (for example, with a probability of 0.8). The participant factors to be balanced in the nested RCT will be age (above or below age 50 years), gender and motor impairment (above or below UHDRS total motor score 40). The randomisation process will be automated via the PACE-HD database.

10 Withdrawal & loss to follow-up

10.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the trial at any time. The participants care will not be affected at any time by declining to participate or withdrawing from the trial.

If a participant initially consents but subsequently withdraws from the trial, clear distinction must be made as to what aspect of the trial the participant is withdrawing from. These aspects could be:

1. Withdrawal from trial intervention
2. Partial withdrawal from further data collection (e.g. some of sample collection, questionnaires, clinical assessments)
3. Complete withdrawal from further data collection
4. Withdrawal of permission to use data already collected

The withdrawal of participant consent shall not affect the trial activities already carried out and the use of data collected prior to participant withdrawal, unless specifically stated by the participant.

It may be important to collect safety data if there is an ongoing safety related event at the time of withdrawal, especially if the participant withdraws because of said safety event. There is specific guidance on this contained in the Participant Information Sheet but briefly:

If a participant does wish to stop taking part in the trial completely, we may ask if they are willing to be seen one last time for an assessment. This assessment would not be for the purposes of collecting research data, but would be a clinical review of the ongoing safety issue to ensure that a resolution had been reached or appropriate clinical management of the issue be put in place for the participant.

A participant may withdraw or be withdrawn from trial intervention for the following reasons:

- Withdrawal of consent for treatment by the participant
- Any alteration in the participant's condition which justifies the discontinuation of the intervention in the Investigator's opinion (such as significantly increased falls or a significant deterioration in the participant's health status [including deterioration in mental state]).

In all instances participants who consent and subsequently withdraw should complete a withdrawal form (see Withdrawal Form in trial pack) or the withdrawal eCRF in the trial database should be completed on the participant's behalf by the researcher/clinician based on information provided by the participant. Withdrawal forms completed by the participant should be sent to

PACEHDtrial@cardiff.ac.uk . Any queries relating to potential withdrawal of a participant should be forwarded by email to: PACEHDTrial@cardiff.ac.uk.

10.2 Loss to follow up

For the longitudinal observation study we do not anticipate a high rate of loss to follow up due the participant's ongoing involvement in Enroll-HD. We will adhere to the Enroll-HD protocol for managing lost to follow up participants in the observational cohort.

For participants in the nested RCT, participants will be deemed to be lost to follow up if they fail to attend more than 4 consecutive coaching contact sessions.

As this is a pragmatic trial, if a participant meets the criterion of lost to follow up, no further direct efforts will be made to engage with that participant. As all participants will be participants of Enroll-HD, we will be able to obtain a proportion of 12-month assessment data for all participants unless they are lost to follow up in the Enroll-HD study. Remote data from FitBit activity monitors will also be collected from those lost to follow up.

11 Trial Intervention

11.1 PACE-HD (for the nested RCT)

Participants randomized to the exercise intervention (n=30) will receive an exercise and physical activity coaching intervention (PACE-HD) over a 12-month period. The PACE-HD intervention is based on interventions developed in two previous studies: *Exert-HD*[4], which utilized a 3 times per week aerobic and strengthening exercise program, and *Engage-HD*[26] intervention, which utilized a coaching program with a purpose-designed workbook to facilitate physical activity and exercise uptake. The PACE-HD intervention is a physical activity behavioural change intervention (based on Engage-HD) that will specifically incorporate promoting aerobic and strengthening exercises based on the Exert-HD intervention. We aim to facilitate exercise uptake over a 12-month period in individuals with HD with the goal to increase both overall physical activity as well as aerobic and strengthening exercise, which has been shown to improve fitness and motor function in people with HD.[4] The intervention will be delivered by licensed physical therapists with experience in delivering exercise-related activities and who will receive specific 1:1 training and ongoing monitoring to deliver the intervention.

The program will consist of 18 face-to-face coaching session (approximately 1 hour) to be held over the course of 12 months. The timing of these sessions will be determined by the participant in consultation with their coach. A coaching manual will be utilized to provide a structured approach to coaching sessions, which will focus on physical activity engagement (specifically aerobic and strengthening exercise) and adherence to exercise. In partnership with the coach, participants will develop physical activity goals that will be monitored and adjusted throughout the program. Participants will be asked to keep monthly physical activity diaries (via paper recording) to record the amount and type of physical activity involvement. These will be returned to local coordinating sites in stamped addressed envelopes provided. Participants will be given wearable activity monitors (Fitbit Charge 2) to be used throughout the 12-month period as a means to facilitate/monitor physical activity and sedentary behaviours. The schedule for receiving messages and the use of the FitBit data will be discussed collaboratively with the patient by the physical activity coach.

The 1:1 coaching intervention will take place in the participant's home or in a rehabilitation facility at each of the sites. Based on our extensive consultations with patients with HD and our prior research in this area,[27] we know that patients with HD need flexibility in terms of access to exercise facilities, and this is critical to successful adherence to an exercise intervention in this population. Therefore, each participant will be provided with a choice of exercise equipment options including a ProForm 440

ES Exercise bike and other exercise equipment (e.g. hand-held weights, medicine balls, therabands) to be utilized for independent sessions. The ProForm bike has been tested in our previous studies, and has been found to be sufficiently sturdy and comfortable for this patient group, who can have excessive abnormal movements (chorea) as well as impaired postural control. Alternatively, participants can choose to exercise in a gym setting of their choice, or to utilize online resources such as exercise videos instead of a stationary bike.

11.2 Adherence

The intervention will be provided by licensed physical therapists. Therapists will provide physical activity coaching, which will be modelled from/on the recently completed *Engage-HD* trial, and focuses on promoting strategies to maintain exercise using a workbook and participant-coach interaction that emphasizes relatedness, autonomy and competence[24]. Caregiver support will be encouraged but is not required. Strategies that support the collaborative regulation theoretical underpinnings of the intervention will be a further focus of the intervention. We will also provide each participant with FitBit physical activity monitors, which can be used to provide reminders for exercising and feedback on physical activity levels to participants, but can also can provide feedback to the physiotherapists regarding the frequency, intensity and duration of independent sessions. For those participants who do not utilize mobile phones or personal computers (which are required to upload FitBit data), or would prefer not to utilize, we will ask permission to utilize text messaging to a caregiver or family member, or to phone the participant. We will also use exercise diaries developed in our feasibility studies, with the option for them to be completed online or via pen and paper. In addition, therapists will have direct contact with participants as needed throughout the course of the trial and will assist participants in setting up schedules and reminders for independent sessions. Exercise diaries will be reviewed by the therapist during every supervised session to facilitate adherence to the program and to monitor progression. Fidelity of the physical activity intervention will be measured using a combination of therapist self-report checklists (indicating whether the content of each of the sessions was consistent with what was specified in the protocol and training manual) and a self-assessment completed by the therapists, at least three times during the course of delivering the intervention to each participant, using a purpose developed rating scale. Although the timescale for completion of the therapist self-assessment will be decided upon by the therapist, we suggest completion after sessions 2, 6 and 15 Participant adherence will be assessed as part of the fidelity assessment in the process evaluation.

11.3 Intervention comparator

Nested RCT

Those participants in the nested RCT randomised 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. They will not receive home visits from the intervention delivery staff (physical therapists), but they will be asked to record their activity monthly in paper diaries which will be sent to them. These participants will also receive monthly prompts via their preferred method of communication (e-mail/ telephone/ text messaging) to remind them to complete and return the diaries to their local coordinating centre in the stamped, addressed envelope provided. Their activity will not be monitored with the use of devices outside the week long activity monitoring period using Gene-activ devices that all participants will undertake.

Observational Cohort

Outside of the baseline and 12-month assessments that will conducted in concert with scheduled annual Enroll-HD assessments, participants in the observational study will have no contact with research staff.

11.4 Defining 'activity as usual'

We will gather data on physical activity levels as well as use of health services as part of the trial assessments. This will give a representation of usual activity in all trial participants.

12 Trial procedures

Recruitment and follow-up:

Participants will be assessed at baseline, at 6 months (for participants of the nested RCT only) and at 12 months. Those enrolled in the observational cohort (n=60) and those taking part in the nested RCT and randomised to the control arm (n=30) will continue to undertake physical activity as usual. Those participants in the nested RCT randomised to receive the intervention (n=30) will receive 12 months of an individualised physical therapy intervention, coached by a physical therapist.

Physical Activity Monitoring

All participants will undergo physical activity monitoring following their baseline and 12 month assessments. Activity will be monitored using Gene-activ devices (which are worn like a wrist watch) for a period of 7 days. Participants will be required to return the Gene-activ device to the site co-ordinator after the monitoring period in a pre-paid, padded envelope provided. Gene-activ devices are not interactive and so the participant will remain blind to the data that is being recorded by the device.

Participants randomised to the intervention arm of the nested RCT will be provided with FitBit Charge 2 device as part of the intervention. These interactive devices will enable participants to track their physical activity and activity goals for the duration of the trial. Data from the FitBit devices will automatically sync to FitBit servers and summary data exports on defined parameters will be sent to the trial team. FitBit devices will not need to be returned at the conclusion of the trial.

Additionally, participants in both arms of the nested RCT will be asked to complete monthly diaries of physical activity. This can be an on-line option (prompted by text message delivery of a link to the on-line form) or a paper based option, dependent on the preference of the participant.

Traditionally, monthly activity data has been collected using a calendar format accessible on-line or on paper. However, completion rates of these formats is typically low. We have designed a novel electronic user interface for participants to provide activity data with the aim of improving completion rates. To test the validity and usefulness of the new design, participants recruited to the RCT arm will be randomised to receive a link to either the existing on-line diary or the novel electronic diary. The implementation of this will not affect activity at sites. A separate Study Within a Trial (SWAT) protocol will be written to define the objectives, outcome measures, randomisation, implementation and analysis of this study.

Data collection/assessments and blinding

All data will be collected by researchers at site and will include but is not limited to; local Enroll-HD coordinators, clinicians and physical therapists delivering the intervention. All assessments will be performed at the research site. Intervention delivery data will be collected at the point of intervention delivery, be that at the research site or participant's home, depending on the participant's preference. Due to the nature of the intervention and the pragmatic design of the nested RCT, researchers collecting assessment data will not be blind to the allocation of participants.

Process Evaluation:

The process evaluation will utilise qualitative data (semi-structured interviews with intervention staff) and quantitative data (structured reflections by members of the research team delivering the intervention and a purpose developed fidelity questionnaire as well as data on completed visits) to assess fidelity (whether the intervention has been delivered as intended and as a measure of quality assurance), and the key mechanisms of change. Participants and their care-givers will be asked to complete a structured questionnaire that focusses on their views of the trial and of the intervention.

We will also attempt to contact any participants who drop out of the intervention to ascertain reasons for discontinuing.

12.1 Assessments

As previously described, we will utilize assessments from the standard Enroll-HD battery. The full Enroll-HD protocol can be found at https://www.enroll-hd.org/enrollhd_documents/Enroll-HD-Protocol-1.0.pdf. In addition to the data gathered as part of the Enroll-HD battery we will collect a number of supplementary measures which are detailed in Tables 1 and 2. Sites must ensure that they conduct the follow up assessment of supplementary measures to coincide with the annual ENROLL-HD visit (± 4 weeks). The full participant schedule of enrolment, assessment and interventions can be found in Table 3.

Longitudinal Observational Study

Participants will be assessed at baseline and again at 12 months

Nested RCT

Participants will be assessed at baseline, 6 months and 12 months.

Table 1: Assessments additional to the standard Enroll-HD test battery for all sites:

Construct	Measure	Time to complete	Time points
Fitness	**Predicted VO2 Max** will be measured during stepwise incremental exercise test[28]. 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	20 min	Baseline, 6 months (RCT only), 12 months

	Watts every two 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 increment, work-rate (Watts), rating of perceived exertion (Borg RPE scale) and heart rate will be recorded for analysis and conversion to predicted VO2 max score.		
Walking endurance	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[29].	10 min	Baseline, 6 months (RCT only) and 12 months
Patient-reported clinical symptoms	HD Pro-Triad[30] will be used to assess disease specific symptoms including cognitive decline, emotional/behavioural dyscontrol and motor dysfunction.	10 min	Baseline and 12 months
Physical Activity Monitoring	Brunel Lifestyle Physical Activity Questionnaire[31] self-report instrument that measures the planned and unplanned dimensions of lifestyle physical activity.	5 minutes	Baseline
	Research-grade physical activity monitors (Gene-activs) will be used for a **7-day physical activity assessment**. [32] Participants will be given the monitors at the consent visit, and will be asked to return them at the baseline visit one week later. They will be requested to wear them for 24 hours a day for the full week, except when showering. Participants will be given the monitors at the end of the assessments, and will be given addressed stamped mailing envelopes to return the monitors one-week later. Data obtained for analysis will include level of overall physical activity, sedentary behavior and sleep patterns. 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.	5 min	Baseline, 6 months (RCT only) and 12 months
	International Physical Activity Questionnaire (Short Form) will be used to assess 7-day physical activity, and to validate with the physical activity monitors.[33]	5 min	Baseline, 6 months (RCT only) and 12 months

Table 2: Assessments additional to the standard Enroll-HD test battery for RCT sites only

Construct	Measure	Time to complete	Time points
Motor and dual task function	The Clinch Token Transfer Test (C3T) is a dual-task assessment of bilateral, upper motor function that consists of three-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	15 min	Baseline and 6 months

	place into a purpose developed box is recorded. The addition of cognitive load increases the task complexity.		
Motor Function	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 based on the application of pre-calibrated and temperature controlled force transducers and 3D position sensors with very high sensitivity and test-retest reliability across sessions and sites in a multicenter clinical trial.	10 min	Baseline and 12 months
Cognitive Function	Q-Cog was developed in TRACK-HD and TRACK-ON-HD where cognitive tasks are related to functionally relevant everyday tasks. 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. Again this offers high sensitivity and test-retest reliability across sessions and sites in a multicenter clinical trial.	20 min	Baseline and 12 months
Self-efficacy	The Lorig Self Efficacy[34] scale will be utilized to measure self-efficacy related to exercise (exercise sub-scale only)	5 min	Baseline, 6 months and 12 months

Table 3. Schedule of enrolment, interventions and assessments (from HRA CTIMP protocol template)

	Screening	Baseline	Intervention			Follow Up
TIMEPOINT** (months)	minus 4 weeks to 0	1	Months 2-6	Month 6	Months 7-12	Month 12
ENROLMENT (OBSERVATIONAL SITES)						
Pre-screening from ENROLL-HD	x					
Eligibility screen (records review)	x					
Informed consent		x				
Registration		x				
EMBEDDED RCT (3 SITES)						
Pre-screening from ENROLL-HD	x					
Eligibility screen (records review)	x					
MUST malnutrition universal screening tool	x	x				
Informed consent	x	x				
Physical Activity Readiness Quesionnaire (Par-Q) safety screening		x				
Registration		x				
Randomisation		x				
LINKED ENROLL-HD DATA (ALL SITES)						
Age		x				
Local CAG high value		x				
Date of HD clinical diagnosis		x				
Ethnicity		x				
Gender		x				
Height		x				
Weight		x				x
BMI		x				x
Medications		x				x
Comorbidities		x				x
Pharmacotherapy		x				x
Non-Pharmacologic Therapies		x				x
UHDRS TMS		x				x
UHDRS TFC		x				x
UHDRS Independence scale		x				x
UHDRS Function Assessment		x				x
Symbol Digit Modality test (numbers correct)		x				x
Verbal fluency category		x				x
Letter Fluency		x				x
Trailmaking		x				x
Stroop word reading test		x				x
Strop colour naming		x				x
Stroop Interference		x				x
CSRI		x				x
HADS-SIS		x				x
Problem Behaviours Assessment (apathy sub domain)		x				x
SF12		x				x
TUG		x				x
30 sec chair stand		x				x
Medication changes since last visit		x				x
Event Reporting						x
PACE-HD STUDY DATA (ALL SITES)						
Physical Fitness predicted VO2		x				x
6 minute walk test		x				x
HD Pro Triad		x				x
Brunel lifestyle physical activity questionnaire		x				
7 day accelerometer based physical activity assessment with sleep diary (debrief interview over phone)		x				x
Self reported physical activity (IPAQ short last 7 days, telephone format)		x				x
Event Reporting						
PACE-HD STUDY DATA (RCT ONLY)						
Physical Fitness predicted VO2		x		x		x
7 day accelerometer based physical activity assessment with sleep diary (debrief interview over phone)		x		x		x
Self reported physical activity (IPAQ short last 7 days, telephone format)		x		x		x
C3T		x		x		
Q Motor assessment battery		x				x
Q Cog assessment battery		x				x
Lorig Self Efficacy Scale (exercise domain)		x		x		x
PHYSICAL INTERVENTION						
Delivery of physical intervention (home visits)		x	xxxx		xxxx	
Text messaging prompts		x	xxxx		xxxx	
Activity monitoring data to record adherence to intervention (FitBit activity data)		x	x		x	
Telephone review (Health and Falls Record)		x	x	x	x	
Adverse event assessments		x	x	x	x	x
USUAL CARE						
Telephone review (Health and Falls Record)		x	x	x	x	
Adverse event assessments		x	x	x	x	x

12.2 Follow-up

Longitudinal observational study

The follow up period is 12 months, in line with the timeline for routine annual Enroll-HD assessments.

Nested RCT

The follow up period is 12 months, in line with the timeline for routine annual Enroll-HD assessments.

13 Safety Reporting

The Principal Investigator is responsible for ensuring that all site staff involved in this trial are familiar with the content of this section. All SAEs must be reported immediately (and within 24 hours of knowledge of the event) by the PI at the participating site to the PACE HD Trial Manager unless the SAE is specified as not requiring immediate reporting (see section 13.2).

13.1 Definitions

Table 4: Adverse event definitions

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical trial participant administered a medicinal product and which are not necessarily caused by or related to that product
Serious Adverse Event (SAE)	Any adverse event that - • Results in death • Is life-threatening* • Required hospitalisation or prolongation of existing hospitalisation** • Results in persistent or significant disability or incapacity • Consists of a congenital anomaly or birth defect • Other medically important condition***

***Note:** The term 'life-threatening' in the definition of serious refers to an event in which the trial participant was at risk of death at the time of the event or it is suspected that used or continued used of the product would result in the subject's death; it does not refer to an event which hypothetically might have caused death if it were more severe.

** **Note:** Hospitalisation is defined as an inpatient admission, regardless of the length of stay, even if the hospitalisation is a precautionary measure for continued observation. Pre-planned hospitalisation e.g. for pre-existing conditions which have not worsened, or elective procedures, does not constitute an SAE.

*** **Note:** other events that may not result in death, are not life-threatening, or do not require hospitalisation, may be considered as an SAE when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

13.2 Trial Specific SAE Reporting requirements

We will only record AEs for the participants taking part in the nested RCT. The proposed interventions are not expected to result in any adverse events. The physical activity intervention does not specifically involve any heavy load-bearing exercise or heavy eccentric muscle activity. However, some minor muscle soreness or muscular strain may occur in the few days following the initiation of a new exercise program or increase physical activity. This would normally resolve spontaneously and would not require any specific interventions or additional medical care, but will be noted as a potential expected related AE if reported.

Falls are an expected AE as part of the clinical condition[35] particularly in the mid-stages of the disease. Any falls will be recorded routinely by the research team and those that result in hospitalisation (thus deemed to be an SAE) will be assessed for causality by the site PI and notified to the trial team.

13.3 Causality

The Principal Investigator (or another delegated suitably qualified clinician or therapist from the trial team registered on the delegation log) will assess each SAE to determine the causal relationship and the Chief Investigator (or another suitably qualified therapist from the Trial Management Group) can also provide this assessment where necessary. Causal relationship will be assessed for the 12-month physical activity intervention.

Table 5: Assessment of Causality

Relationship	Description	Reasonable possibility that the SAE may have been caused by the intervention?
Unrelated	There is no evidence of any causal relationship with the trial/intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the trial/intervention (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition, other concomitant treatment).	No
Possible	There is some evidence to suggest a causal relationship with the trial/intervention (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the participant's clinical condition, other concomitant treatments).	Yes
Probable	There is evidence to suggest a causal relationship and the influence of other factors is unlikely.	Yes
Definite	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	Yes

The causality assessment given by the Principal Investigator (or delegate) cannot be downgraded by the Chief Investigator (or delegate), and in the case of disagreement both opinions will be provided.

13.4 Reporting procedures

13.4.1 Participating Site Responsibilities

The PI (or delegated suitably qualified clinician or therapist from the site trial team registered on the delegation log) should complete the safety reporting form in the trial database to acknowledge that he/she has performed the seriousness and causality assessments. Investigators should also report SAEs to their own local authorities in accordance with local practice.

A completed SAE form for all events requiring immediate reporting should be submitted via the trial database or completed on a paper form and emailed to the CTR within 24 hours of knowledge of the event, if the database is unavailable. Submission of the form via the trial database will generate an automatic alert to the trial team. A separate form must be used to report each event, irrespective of whether or not the events had the same date of onset.

The participant will be identified only by HDID and trial PID. The participant's name should not be used on any correspondence.

It is also required that sites respond to and clarify any queries raised on any reported SAEs and report any additional information as and when it becomes available through to the resolution of the event. Additionally, the CTR may request additional information relating to any SAEs and the site should provide as much information as is available to them in order to resolve these queries.

Serious Adverse Event (SAE) Reporting

Trial Database: https://pacehd.sewtudb.cf.ac.uk/login/

email address: PACEHDTrial@cardiff.ac.uk

Serious adverse events should be reported from the time of the baseline assessment, throughout the intervention period. SAEs do not need to be reported if they occur during the week long follow up period of activity monitoring.

An SAE form is not considered as complete unless the following details are provided:

- Full participant trial number
- An Adverse Event
- A completed assessment of the seriousness, and causality as performed by the PI (or another suitably qualified clinician or therapist from the site trial team registered on the delegation log).

If any of these details are missing, the site will be contacted and the information must be provided by the site to the CTR within 24 hours. All other AEs should be reported in the adverse event reporting section of the database following the eCRF procedure described in Section 16.

13.4.2 The CTR Responsibilities

Following the initial report, all SAEs should be followed up to resolution wherever possible, and further information may be requested by the CTR. Follow up information must be provided on a new SAE form. The CTR should continue reporting SAEs until the participant receives the last part of the intervention. Once an SAE is received at the CTR, it will be evaluated by staff at the CTR and sent to the Chief Investigator (or their delegate) for an assessment of expectedness.

13.5 Contraception and pregnancy

Exercise and physical activity is not contra-indicated in pregnancy, Current clinical evidence points towards the maintenance of an exercise of a program during pregnancy as beneficial to both mother and child, therefore, this pragmatic trial will not advise that pregnancy be prevented during this trial.

13.5.1 Contraception

Women of Child Bearing Potential (WOCBP) entering into this trial will not be asked to take contraception during the trial as a condition of participation.

13.5.2 Pregnancy reporting whilst participating in the trial

Pregnancy occurring whilst participating in the trial, is not considered an SAE, however, an issue with the pregnancy, a congenital anomaly or birth defect is. Other cases (e.g. termination of pregnancy without information on congenital malformation, and reports of pregnancy exposure without outcome data) should not normally be reported as such. When pregnancy occurs, this should be followed up until the end of the participant's involvement in the trial or until the end of pregnancy, whether that is a live birth, abortion etc. Without follow-up of the pregnancy, it would not be possible for the CTR to know if a pregnancy issue, congenital anomaly or birth defect occurred, and therefore if there was an SAE that must be included in the safety evaluation of the intervention. Information on a pregnancy in a trial participant will be captured on the CTR Pregnancy Report Form supplied to sites by the CTR.

Sites should report any pregnancy occurring during the course of the intervention. For any pregnancies occurring in participants of the longitudinal observational study these do not need to be reported. Issues occurring during the pregnancy, congenital anomalies or birth defects are considered an SAE and so these events must also be reported to the CTR on a trial-specific SAE form and should be submitted to the CTR within the timeframes stipulated for SAE reporting.

13.6 Urgent Safety Measures (USMs)

An urgent safety measure is an action that the Sponsor or Chief Investigator may carry out in order to protect the subjects of a trial against any immediate hazard to their health or safety. It is extremely unlikely that any urgent safety measures should be required for this trial, but any urgent safety measure relating to this trial that does occur must be notified to the local Institutional Review Board (IRB) immediately by telephone, and in any event within 3 days in writing, that such a measure has been taken. USMs reported to the CTR will be handled according to CTR processes.

14 Statistical considerations

14.1 Randomisation

A minimisation technique will be used for randomisation to allow for balancing of age (above or below age 50 years) and motor impairment (above or below UHDRS total motor score 40) at baseline. The randomisation will be stratified by country. A Randomisation schedule will outline all randomisation procedures, implementation and back-up system.

14.2 Blinding

There will be no blinding of participants or assessors in the nested RCT. The nature of the intervention means that participants cannot be blinded however there are a range of quantitative outcomes that will be collected in an attempt to minimise bias.

14.3 Sample size

The primary outcome for this trial is feasibility of a within cohort nested RCT of a 12-month exercise intervention in terms of; data completeness, recruitment, retention, fidelity and acceptability. For a total sample size of 120 participants recruited into the cohort study we are able to determine a 95% confidence interval for 70% retention rate to within +/- 8.2%.

In line with the primary feasibility objectives of the trial a formal calculation has not been carried out to determine the sample size for the RCT. Formal hypotheses testing will not be carried out and only effect sizes and 95% confidence intervals will be provided for the interpretation of outcomes

.

14.4 Missing, unused & spurious data

All data will be checked prior to analysis and cleaned following standard procedures outlined in the data management and statistical analysis plans.

14.5 Procedures for reporting deviation(s) from the original SAP

These will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

14.6 Termination of the trial

Circumstances surrounding the enforced withdrawal of individual participants by the site researchers can be found in section 10.1

14.7 Inclusion in analysis

All participants enrolled into the cohort study will be included in the analysis of the cohort study results unless they specifically request to withdraw their data from analyses. Additionally, all participants randomised in the nested RCT will be included in the analysis of the RCT results unless they specifically request to withdraw their data.

15 Analysis

15.1 Main analysis

Descriptive statistics will summarise the key demographics and patient characteristics of the cohort. The formal analysis will be conducted in two parts.

a. Feasibility

Summary data for recruitment, retention and data completeness will be tabulated for the cohort and nested RCT. Adherence rates, safety and fidelity will also be summarised for the RCT.

b. RCT

The individually randomised data from the three sites will be explored.

The analysis will compare

I. **Linked Enroll-HD data** - for participants between the two groups at 1 year
II. **PACE-HD trial data** (see section 12.1)

Linear models will be used for key continuous outcomes, controlling for individual participant characteristics used to balance the randomisation as baseline covariates. Treatment effects will be summarised using regression coefficients, 95% confidence intervals and standardised effect sizes. Standard diagnostics will be performed to ensure adequate model fit (including inspecting fitted versus residual plots). The analysis will be intention to treat and complete case.

Analysis of secondary outcomes will proceed similarly, with linear regression used for continuous outcomes and logistic regression for dichotomous outcomes. A mediation analysis will be performed on the physical fitness measure recorded at 6 months. No inflation for clustering has been included in the power calculation however a sensitivity analysis will be conducted using hierarchical modelling to explore the extent of clustering in the primary outcome variable by site.

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 at 12 months will indicate that the intervention is suitable for further evaluation without modification.

15.2 Exploratory analyses

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 in relation to fitness at 6 and 12 months. We will also explore data on usual activity from the range of physical activity self-report assessments in relation to blinded Geneactiv activity monitoring data.

Principal Component Analysis will be used to explore the validity of a composite outcome for HD. The composite will be based on motor and cognitive outcomes and will be compared between arms using confidence intervals.

To explore the added value of augmenting a randomised control group with non-randomised activity as usual cohort data, all analyses will be repeated including the three non-randomised sites as additional control participants. The use of propensity score weighting for this approach will also be explored.

Specifically, we will 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. Since Enroll-HD does not capture sufficiently detailed data on physical activity and fitness in HD it will in essence serve as a useful control/reference cohort who are participating in "usual physical activity".

The results from the "RCT control group" and "reference" group, will be compared via a sensitivity analyses. The propensity score methods will allow us to create groups that are balanced and therefore the bias associated with observational data is minimised. The results of these two approaches will be compared and contrasted and appropriate inference made.

15.3 Process analyses

Semi-structured interviews will be audio-recorded, transcribed and analysed thematically. All quantitative data will be summarised using frequency based data.

16 Data Management

Source data for the PACE-HD trial will be obtained from three principal components:

1) Import of Linked Enroll-HD data
2) Import of activity data from a) FitBit and b) Geneactiv activity monitors.
3) Completion of electronic CRFs

Enroll-HD Data

All participants in PACE-HD will be involved in the Enroll-HD study. Assessment data will be collected as part of Enroll-HD via the Enroll-HD platform. The PACE-HD trial will receive data exports from Enroll-HD for all PACE-HD participating sites on a minimum of three occasions; 1) after recruitment of 5 participants per site, 2) at the close of recruitment and 3) when the last participant has completed the 12 month follow up assessment. Data exports will contain coded datasets identified by the HDID. Data exports will be imported into the PACE-HD database.

Activity Monitor Data

Two types of physical activity monitoring data will be used.

1) **Geneactiv devices** will evaluate 7-day physical activity for all participants in both the cohort study and in the RCT, but participants will be blinded to any information (there is no LCD monitor and no means for participants to access any information collected by these devices). When Geneactiv devices have been returned to site by the participant at the end of the 7-day recording period, raw data will be extracted from the device at site. This anonymous data will be transferred to the central trial team via a secure and encrypted file transfer system such as Fastfile. Data will be identified by trial participant number. The central trial team will apply a pre-programmed algorithm to the raw data to obtain the desired measures for the PACE-HD trial. The transformed data will then be automatically uploaded to the PACE-HD database.
2) Fitbit Physical Activity Monitors will be used to obtain physical activity, heart rate and sleep data only for participants in the RCT who are randomised to receive the physical activity intervention. Data from the FitBits will automatically upload to the FitBit research data platform, FitaBase. Anonymous data exports of summary (not raw) will be received on a monthly basis for upload into the PACE-HD database. Individual data sets will be identified by the trial participant number and HDID.

All data rights and usage (for imported data) will be covered by contractual agreement. Details for the collection of source data via electronic and paper CRFs are detailed in section 16.1 below. Further detail on data management can be found in the PACE-HD data management plan.

Table 6 List of trial data to be recorded and the location of that source data

Trial data	Source Data											
	Screening Log	Consent Form	Electronic System (PACE-HD database)	Paper CRF (as back up)	ENROLL-HD data export	FitaBase Data export	Q motor data export	GeneActiv Watch (Secure electronic storage)	Participant Diary	Questionnaire	Interview	SAE form (as back up)
Pre-Screening	X											
Eligibility Screening	X											
Informed Consent		X										
Registration			X	X								
Safety screening data (RCT only)			X	X								
Randomisation (RCT only)			X	X								
Linked ENROLL-HD data					X							
PACE-HD Study data			X	X								
PACE-HD Study data (RCT only)			X	X			X (Qmotor data only)	X (Geneactiv data only)				
Fit Bit activity data (RCT only)						X						
Intervention fidelity (participant diaries) (RCT only)			X						X			
Intervention Fidelity [coach] (RCT only)			X	X								
Health and Falls Record (RCT only)			X									
Adverse events			X									X
Process Evaluation										X	X	
Participant withdrawal			X	X								

16.1 Completion of CRFs

The mode of data collection for PACE-HD will be via direct data entry into electronic CRFs via the individual researcher log-ins to the on-line trial database. For instances where access to the on-line database is not possible, a paper copy of each CRF will be provided in the site file for completion by researchers at site. If paper copies of the CRF are used, the data from these must be entered into the eCRF within one week of data collection.

16.1.1 Electronic CRFs

It is intended to develop data recording for this trial as a web-based system. This is a secure encrypted system accessed by an institutional password, and complies with Data Protection Act standards. The system can be accessed on:

https://pacehd.sewtudb.cf.ac.uk/login/

Sites will be provided with a tablet computer to facilitate data entry. A user password will be supplied to investigators upon completion of all processes required prior to opening.

Web-based data collection forms should be completed as follows:

For all participants:

- Registration
- Baseline assessment to include;
    - predicted VO_2max
    - Q motor test battery
    - 6-minute walk
    - HD Pro-Triad
    - C3T
    - IPAQ
    - Lorig self-efficacy (exercise sub-domain only)

- Brunel physical activity questionnaire
- 12-month assessment (as detailed above)

Additional forms for participants in the nested RCT to include:

- Randomisation
- Home visit record (up to 18 occasions)
- Telephone call record (up to 18 occasions)
- Text message prompt record (up to 24 occasions)
- Staff intervention fidelity checklist
- 6-month assessment (as detailed above)

All electronic CRFs should be completed in real time at the point of data collection (see the section 16.1.2. for when real-time data entry is not possible).

The database is constructed with inbuilt data validation systems to prevent erroneous values from being entered. Specific prompts and alerts included in the database will flag any missing data when the researcher tries to complete the form and users inputting data will not be able to move on until all data fields are filled. For further details on data management please refer to the PACE-HD data management plan.

16.1.2 Paper CRFs

Paper versions of the electronic CRFs will be made available in the Investigator site file in the unlikely event that researchers at site are unable to access the PACE-HD database.

If a researcher is unable to upload the data into the PACE-HD database at the time of collection, the data should be collected on the paper version of the CRF for subsequent transcription into the database as soon as access is possible. This should be completed within one week of the data collection occurring. Any data captured in paper CRFs do not need to be returned to the central trial team, but should be stored securely with the ISF.

Participants in the nested RCT will be required to complete the exercise diary on a paper form and return to the local research team on a monthly basis. The local research team will be asked to enter the data into the trial database. The paper exercise diaries should then be stored at site and do not need to be returned to the CTR.

17 Protocol/GCP non-compliance

The Principal Investigator should report any non-compliance of the trial protocol or the conditions and principles of Good Clinical Practice to the CTR in writing as soon as they become aware of it.

18 End of Trial definition

Longitudinal Observational Study

For participants involved in the observational part of the trial, the end of the trial will be defined by their last visit which will be the 12-month assessment performed in line with their annual Enroll-HD assessment.

Nested RCT

The intervention phase will be followed by a follow-up period which will continue for one week after the last participant completes the intervention. This follow up will consist solely of activity monitoring using a wrist worn monitoring device (e.g. an activity watch). On conclusion of this week long monitoring period, the participant's involvement in the trial will end.

The end of the trial is defined as the date of final data capture to meet the trial endpoints. In this case end of trial is defined as upload of the final activity monitoring data into the trial database. Sponsor must notify the local IRBs of the end of a clinical trial in accordance with local requirements.

20 Archiving

The TMF and TSF containing essential documents will be archived at an approved external storage facility for a minimum of 5 years. The CTR will archive the TMF and TSFs on behalf of the Sponsor. The Principal Investigator is responsible for archival of the ISF at site on approval from Sponsor and according to local governance arrangements. Essential documents pertaining to the trial shall not be destroyed without permission from the Sponsor.

21 Regulatory Considerations

21.1 Ethical and governance approval

This protocol has been reviewed by the IRB responsible for ethical oversight of research in each country where trial sites are located, and approval obtained.

Approval will be obtained from the host care organisation who will consider local governance requirements and site feasibility. The Research Governance approval of the host care organisation must be obtained before recruitment of participants within that host care organisation.

21.2 Data Protection

The CTR will act to preserve participant confidentiality and will not disclose or reproduce any information by which participants could be identified, except where specific consent is obtained. Data will be stored in a secure manner and will be registered in accordance with the Data Protection Act 1998. The data custodian for this trial is the Chief Investigator.

All data collection will be coded, with individual data sets identified by trial identification number and the HDID from Enroll-HD. No personal data will be collected in the PACE-HD trial. Data shared between participating organisations and the Cure Huntington's Disease Initiative (CHDI) Foundation who govern the ENROLL-HD platform, will be done so anonymously.

All data will be stored in the trial specific database detailed in section 16.0, including all Enroll-HD and Fitabase data imports. The database will be held and maintained on secure servers at Cardiff University that are subject to automatic back-up. Access to the database is password protected and permission to access all data is restricted to specific qualified personnel within the core trial team.

No paper copies of collected data will be stored centrally at the CTR. Any data collected on paper at site will be stored securely at site according to local regulation. This will need to be in a secure environment and protected by at least two physical barriers (e.g. a locked filing cabinet in a locked office).

21.3 Indemnity

- Non-negligent harm: This trial is an academic, investigator-led and designed trial, coordinated by the CTR. The Chief Investigator, local Investigators and coordinating centre do not hold insurance against claims for compensation for injury caused by participation in a clinical trial and they cannot

offer any indemnity. The Association of the British Pharmaceutical Industry (ABPI) guidelines will not apply.

- Negligent harm: Where studies are carried out in a hospital, the hospital continues to have a duty of care to a participant being treated within the hospital, whether or not the participant is participating in this trial. Cardiff University does not accept liability for any breach in the other hospital's duty of care, or any negligence on the part of employees of hospitals. The Sponsor shall indemnify the site against claims arising from the negligent acts and/or omissions of the Sponsor or its employees in connection with the Clinical Trial (including the design of the Protocol to the extent that the Protocol was designed solely by the Sponsor and the Site has adhered to the approved version of the Protocol) save to the extent that any such claim is the result of negligence on the part of the Site or its employees.

21.4 Trial sponsorship

Cardiff University will act as Sponsor for trial. Delegated responsibilities will be assigned to the sites taking part in this trial. The Sponsor has delegated certain responsibilities to Cardiff University (CTR), the Chief Investigators, Principal Investigators, host sites and other stakeholder organisations as appropriate in accordance with the relevant agreement that is informed by regulation and trial type. and can be found in the memorandum of understanding between the sponsor and the CTR. Responsibilities delegated to the CTR by sponsor can be found in the trial delegation log and in the memorandum of understanding.

21.5 Funding

This trial is funded by the Jacques and Gloria Gossweiler Foundation. Sites will receive payment for site set-up, trial coordination and funds to purchase the equipment (or gym membership) necessary to deliver the intervention to participants. Equipment such as the stationary bike, Geneactiv activity monitors and FitBit activity monitors will be provided to site directly. The precise financial arrangements will be detailed in individual site agreements.

22 Trial management

The PACE-HD Trial will be managed through the convening of several management groups tp provide regulatory, scientific and clinical oversight. These will include a project team (consisting of the core trial team involved in the day to day management of the trial, which will meet on a monthly or bi-weekly basis according to the stage of the trial) meetings, a trial management group and a trial steering committee.

22.1 TMG (Trial Management Group)

TMG will be convened to provide guidance on the running of the trial and to act as a decision making body for any issues that occur during the trial. The TMG will consist of all co-applicants, members of the Enroll-HD platform team and a Public and Patient Representative. TMG members will be required to sign up to the remit and conditions as set out in the TMG Charter. For full details of TMG membership and remit please refer to the TMG charter.

TMG meetings will occur monthly during the trial including set-up, analysis and close down. All meetings will be fully minuted and a record of the minutes will be held in the TMF.

22.2 TSC (Trial Steering Committee)

TSC members will be required to sign up to the remit and conditions as set out in the TSC Charter. Then TSC will consist of at least one independent statistician and one independent researcher with experience in physical therapy research. The TSC Will be chaired by an independent researcher with knowledge in the disease specific area. For specific details of the TSC membership, refer to the TSC charter.

The TSC will be expected to meet twice a year, with the inaugural meeting occurring prior to trial opening and the final meeting convened to discuss the trial results prior to publication and dissemination.

22.3 DMC (Data Monitoring Committee)

For this trial, no formal DMC will be convened. Any specific issues relating to safety or data integrity will be discussed at the monthly TMG in the first instance and escalated to the TSC for further discussion and oversight if deemed necessary.

23 Quality Control and Assurance

23.1 Monitoring

The clinical trial risk assessment has been used to determine the intensity and focus of central and on-site monitoring activity in the PACE-HD trial. Low + monitoring levels will be employed and are fully documented in the trial monitoring plan. The monitoring plan will also detail the involvement of ENROLL-HD monitors in central and on-site monitoring.

Investigators should agree to allow trial related monitoring, including audits and regulatory inspections, by providing direct access to source data/documents as required. Participant consent for this will be obtained.

Findings generated from on-site and central monitoring will be shared with the Sponsor, CI, PI & local regulatory bodies.

23.2 Audits & inspections

The trial is participant to inspection by country specific regulatory bodies. The trial may also be participant to inspection and audit by Cardiff University under their remit as Sponsor.

24 Publication policy

All publications and presentations relating to the trial will be authorised by the Trial Management Group.

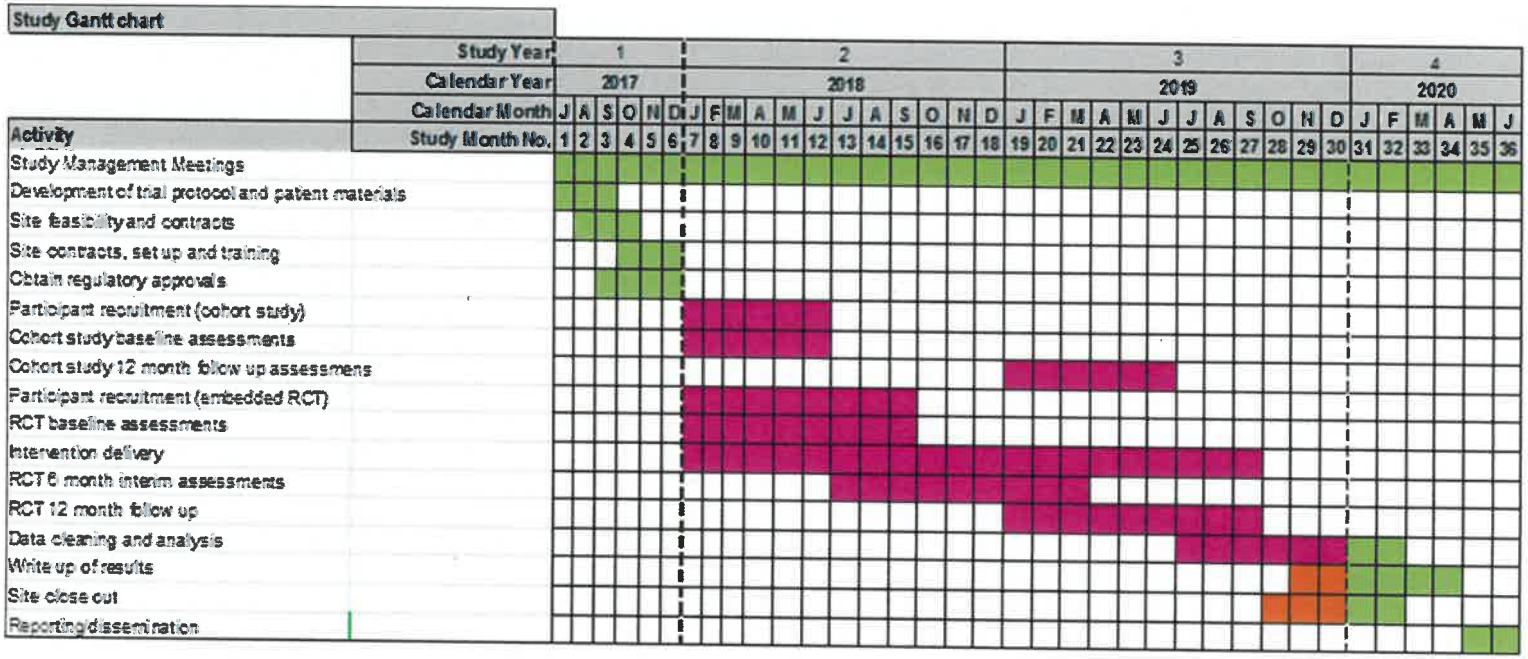
Authorship for presentations and publications will be decided by the TMG (all trial team members will be given the opportunity to contribute to publications) and we will follow the published BMJ criteria for authorship for each individual publication. Details of all planned publications and presentations, along with the criteria for authorship, can be found in the PACE-HD trial publication policy.

The final trial data will be shared with the CHDI Foundation, but the PACE-HD TMG will reserve the right to be the first to publish the trial results. Further details can be found in the PACE-HD publication policy.

In addition to journal publication, the final results of the trial will be fed back to participants via newsletter at the relevant participating sites.

25 Milestones

Figure 1: Key Trial Timelines



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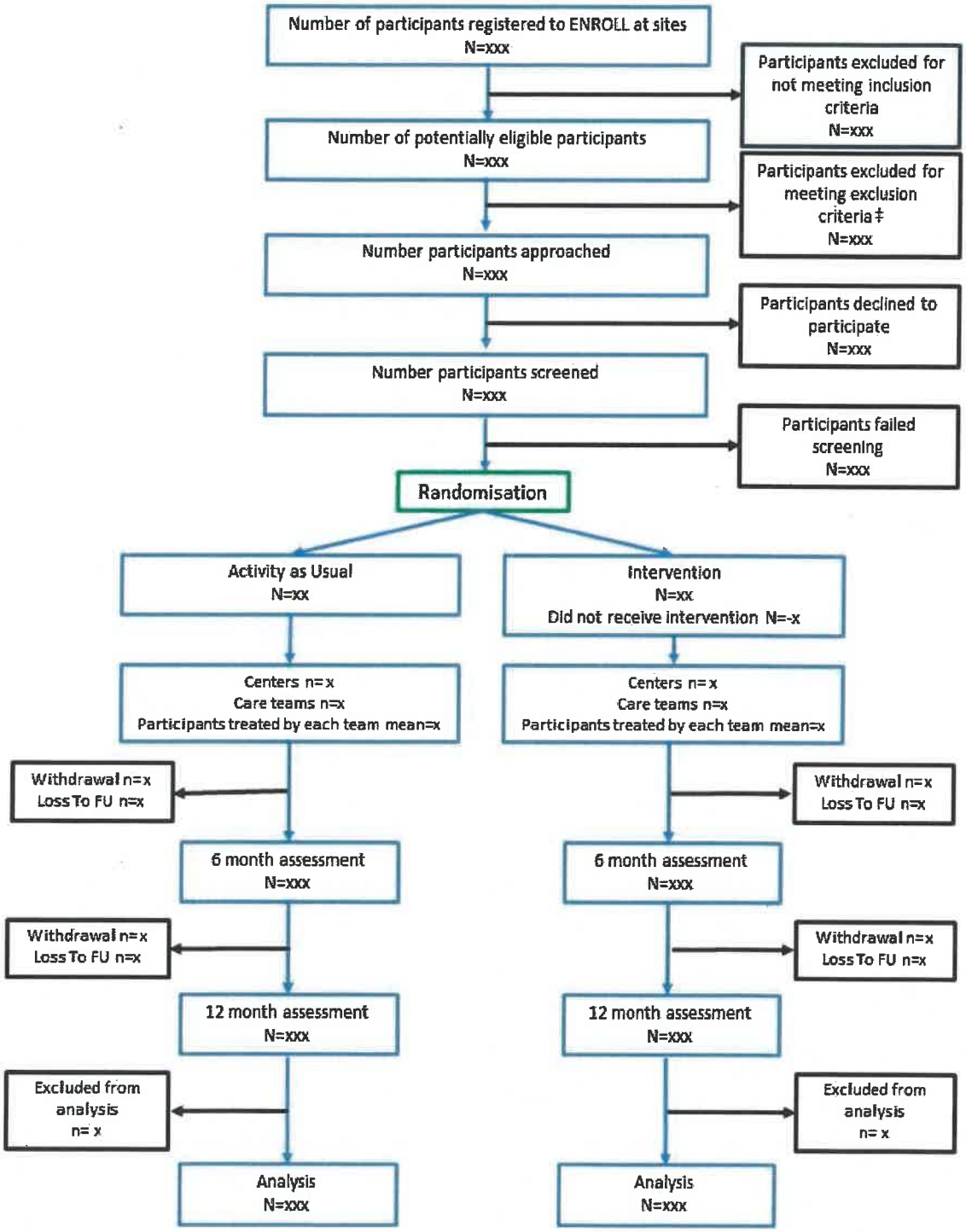
27 Appendices

APPENDIX I: CONSORT Diagram for PACE-HD



‡ - list n for each exclusion criteria