DOMINO-HD

MULTI-DOMAIN LIFESTYLE TARGETS FOR IMPROVING PROGNOSIS IN HUNTINGTON'S DISEASE (DOMINO-HD)

DOMINO-HD: An observational study providing new insights into lifestyle and genetic risk factors in Huntington's disease

PARTNER SITE MASTER PROTOCOL TEMPLATE

PROTOCOL VERSION 2.0~~1.1~~

08~~27~~/0~~21~~/2021

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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 CTR'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 publicly 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.

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Monica Busse	Monica Busse	**21/01/2021**
Name	**Signature**	**Date**
Study Sponsor :		
Chris Shaw		
Name	**Signature**	**Date**
Partner Site Principal Investigator:		
Name	**Signature**	**Date**

General Information. This protocol describes the DOMINO-HD Study, and provides information about the procedures for entering participants into the study. 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 study. Problems relating to the study should be referred, in the first instance, to CTR.

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Study Co-ordination:

The DOMINO-HD study is being coordinated by the Centre for Trials Research (CTR), Cardiff University. This protocol has been developed by the DOMINO-HD Study Management Group (SMG). For all queries please contact the DOMINO-HD team through the main Study email address. Any clinical queries will be directed through the Study Manager to either the Chief Investigator or Co-Investigators.

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Clinical queries:

Protocol queries
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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 study database (https://dominohd.sewtudb.cf.ac.uk/login/)) or by completing a paper SAE form and emailing to dominohd@cardiff.ac.uk by the responsible clinician / researcher within 24 hours of becoming aware of the event (See section 16 for more details).

Table of Contents

Glossary of abbreviations

AAO	Age at onset
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
CU	Cardiff University
EAT-10	Eating Assessment Tool
EPIC-FFQ	European Prospective Integration into Cancer and Nutrition Food Frequency Questionnaire
ES	Effect Size
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GWAS	Genome Wide Association Study
HD	Huntington's disease
IC	Informed consent
IPAQ	International Physical Activity Questionnaire
IRB	Institutional Review Board
ISF	Investigator Site File
MICE	Multiple Imputation Derived Equation
MUST	Malnutrition Universal Screening Tool
PAR	Physical Activity Recall
PI	Principal Investigator
PIS	Participant Information Sheet
QL (QoL)	Quality of Life
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
SMF	Study Master File
SMG	Study Management Group
TWAS	Trial Within a Study

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.	Protocol version no.	Date issued	Summary of changes made since previous version
Non substantial amendment 1	1.1	27/01/2021	Minor change to timing of completion of outcome measures for optional 7 day in home assessment
Non-substantial amendment 2	1.2	08/02/2021	Optional truncation of 12-month assessment

2 Synopsis

Short title	Multi-**Dom**ain Lifestyle Targets for **I**mproving Prog**no**sis in **H**untington's **D**isease
Acronym	DOMINO-HD
Study type:	Observational
Funder and ref.	Joint Program for Neurodegenerative Disorders
Planned sample size	Minimum 60 participants with HD (up to 90) per site to achieve a total target sample size of 300 participants across all sites
Planned number of sites	5
National or International	International
Inclusion criteria	• Diagnosis of HD confirmed by genetic testing. • Above the age of 18. • Diagnostic confidence level (DCL) 3 and 4 (which can include both pre-motor [late prodromal] or motor manifest HD). • Self-ambulatory. • A participant (current or newly enrolled) in the Enroll-HD study (with a preference for those who have been genotyped in GWAS3-5 or are to be genotyped in GWAS6).
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. • Severe medical conditions such as unstable or progressive heart disease, uncontrolled diabetes, severe liver, kidney or thyroid dysfunction or similar medical conditions. • Any acute or unstable psychiatric condition • Unable to tolerate long-term wear of activity monitor. • Inability or unwillingness of participant to give written informed consent. • No access to a smartphone. • Not willing to allow the research team to install Apps on their smartphone related to the study.
Participation in study	12 months
Planned study period	30 months
Primary objective	Establish the feasibility of linking lifestyle factors, with genetic risk factors to explore their interplay with HD symptom severity.
Secondary objectives	i. Establish feasibility and acceptability of using digital technologies to consistently collect information directly from people with HD about their physical activity, sleep and diet. ii. Evaluate how appropriate commercially available activity trackers are to measure physical activity and sleep in people with HD. iii. Design lifestyle and / or behavioural interventions aimed at improving the quality of life of people with HD.
Exploratory objectives	These are site specific and outlined as part of each sub-study in Appendix (A)

Study summary & schema

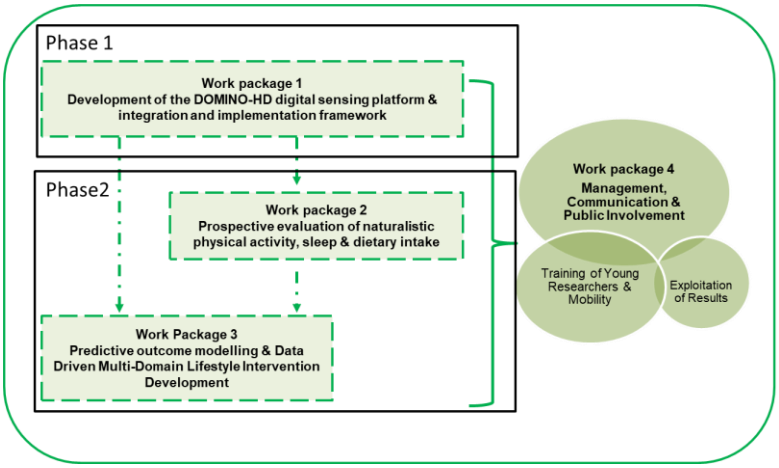
The activities described in this protocol form part of a larger consortium study through the EU joint programme-Neurodegenerative Disease, involving 7 partners, all of which contribute in different ways to overall consortium success.

Initial work across the consortium will be site specific, with partners contributing in different ways to demonstrate the feasibility of a digital sensing platform capable of providing meaningful and user acceptable objective monitoring of physical activity, sleep and diet in Huntington's disease (Phase 1: **Work Package 1**). A brief synopsis of each sub-study is provided in Appendix A. Each sub-study will have a separate protocol and independent IRB approvals. Cardiff University are providing sponsorship for all activities outlined in Appendix A as part of Phase 1.

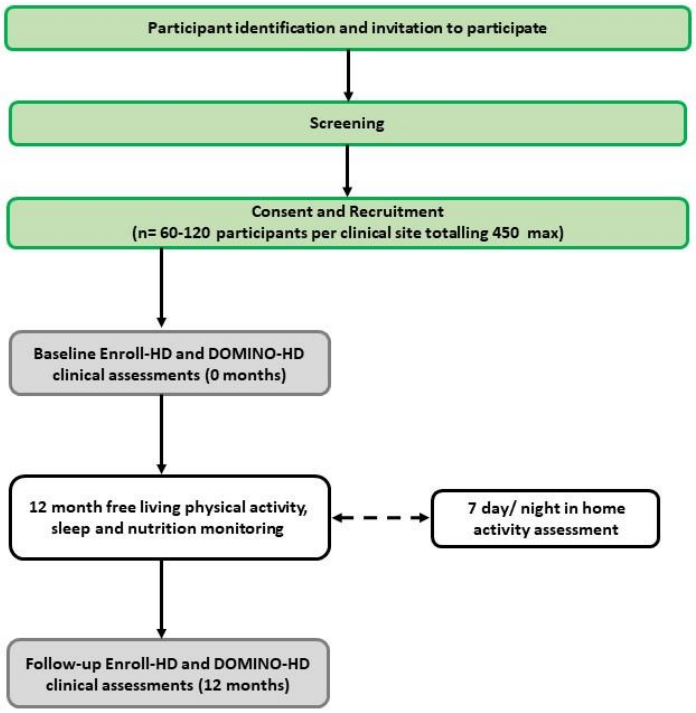
A consortium wide clinical study will then be undertaken (and is the focus of this protocol), with [specific site details] being one of five clinical sites across Europe to participate in 12-month observational study with a combined target of recruiting 300-450 people with HD (Phase 2: Work Package 2). A digital platform and objective clinical assessment methods will be developed as one component of the Phase 1 study activities. Participants across all clinical sites will be recruited through Enroll-HD, 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/). This will allow DOMINO-HD research data to be combined with genomic data and comprehensive clinical assessment data captured via Enroll-HD (full Enroll-HD protocol https://www.enroll-hd.org/enrollhd_documents/Enroll-HD-Protocol-1.0.pdf). Cardiff will be the central data controller for all the observational data collected across all clinical sites which will be combined and used to inform predictive outcome modelling and intervention development (**Work Package 3**). As coordinator, Cardiff plays a pivotal role in the cross-cutting activities in **Work Package 4** that include management, communication and public involvement whilst also developing plans for exploitation and communication of results and the training of young researchers.

This protocol refers to the research being undertaken at [site specific details] only, with remaining partners obtaining local IRB approval as appropriate.

3.1 Study schema



3.2 Participant flow diagram



3.3 Study lay summary

This research will help to understand Huntington's disease by monitoring how the disease appears and changes over time in people with HD, linking new insights into behaviour and lifestyle to clinical assessments of HD and genetic risk.

An observational study will be performed in [site specific details] as part of Phase 2 (Work Package 2), involving participants with a confirmed diagnosis of HD (minimum target of 60, potential maximum of 120 participants). These participants will be asked to take part in a 12-month study where information on their physical activity, sleep and diet habits will be collected using the digital platform developed as part of the broader DOMINO-HD project. We will ensure that all participants are familiar with the technology, are happy using them and have enough support from the research team whilst using them during their daily lives.

All participants will be recruited through an on-going worldwide observational study (Enroll-HD) where they complete annual standard clinical assessments of HD symptoms and genetic profiling as part of long-term monitoring of their disease. With the observational study lasting 12-months, participants will perform the annual Enroll-HD assessments at the start (baseline) and again at the end of the study (12-month follow up). Additional DOMINO-HD specific clinical assessments will also be performed at these time points.

The data collected through the observational study will be combined with data collected at 4 additional partner clinical sites who will perform the same protocol following local IRB approval. This will result in a combined minimum target dataset of 300-450 participants (managed centrally in Cardiff) and will be analysed to examine how lifestyle factors (such as the amount of physical activity performed, the amount of sleep participants get and the type of diet they have) may be associated with disease progression. This work will include statistical modelling to identify factors that may be altered and that influence outcomes in HD. Genetic risk factors, including CAG repeat length, and other known modifiers will be included in this analysis. Once this has been performed and the important lifestyle factors have been identified, an intervention will be developed so that future studies can see whether disease progression can be modified as a result of changing behaviour and lifestyle. This process will form the basis of Work Package 3 and will be heavily influenced by feedback from people with HD and their families and carers so that the intervention is designed in a way that is acceptable and feasible to those it is targeting.

4 Background

HD is the most common monogenetic disease acting on the central nervous system with a prevalence of 6-13/100,000 in the general population[1]. It is a progressive autosomal dominant inherited neurodegenerative disorder with death occurring 15 to 30 years after onset of symptoms. The personal, social and economic consequences of HD are devastating, primarily due to loss of independence and increasing societal isolation. The gene mutation is a cysteine adenine guanine (CAG) repeat expansion in the *huntingtin* gene on chromosome 4, accounting for approximately half of the variance in age at onset (AAO)[2]. Although, in recent years, there has been great excitement

over newly identified genetic polymorphisms[3–6], our primary focus is on the role of environmental factors.

HD pathology is principally characterised by death of the medium spiny neurons of the striatum and thus disruption of corticostriatal pathways with progressive and severe cognitive, motor and behavioural dysfunction. Other neurons within the cerebral cortex are also vulnerable leading to extended involvement of central nervous system structures over time[7]. Although clinical translation of potential disease modifying treatments, such as gene-silencing or regenerative medicine approaches, are underway, these approaches are experimental and efficacy and clinical benefit still needs to be established. Complementing these ongoing efforts to alter the relentless progression of HD, it is imperative to identify novel, evidence-based health interventions and strategies that may complement one another to reduce the impact of the disease, across the course of its development.

4.1 Environmental factors in HD

The importance of the role of environmental factors in age at onset (AAO) in clinical populations (based on the findings from the Venezuelan HD kindred study[2]), is underpinned by reports of differing phenotypic expression in monozygotic twins with HD[8–10]. Indeed, it has been suggested that environmental factors (such as physical activity and diet) may have at least as much impact on AAO[11] as genetic modifiers.

4.2 Physical activity and HD

A detailed study of leisure and non-leisure activities of individuals with HD was previously conducted with the aim of establishing lifestyle factors influencing AAO[12]. The authors conducted retrospective interviews with people with HD and based on the recall data over 3 decades computed a lifetime leisure (physical, intellectual and passive) and non-leisure (education, occupation and domestic activity) score as well as a composite lifestyle score for passive, intellectual and physical activity. Multi-level modelling was used to investigate these composite factors and the authors concluded that earlier age of onset was associated with a more passive lifestyle. Whilst informative, a clear limitation of this methodology was the use of recall to produce the lifestyle score. Additional clinical studies provide preliminary support for the benefits of exercise and physical activity in terms of motor function, gait speed, and balance[13–16]. In all of these studies, a major concern, however, is the inability to accurately assess levels of physical activity in daily living. There is an increasing interest in the potential for wearable technology to provide detailed phenotypical information about function and physical activity in HD, however the relatively few published studies involving commercially available devices are limited by the lack of disease specific validations[17–19].

4.3 Sleep and HD

A number of brain regions affected by HD play a role in sleep and circadian rhythms[3]. Sleep disturbance has been recognised as one of the earliest features of clinical manifestation and contributory to early cognitive dysfunction of HD[20,21]. Sleep disruption may also be a general mechanism promoting neurodegeneration[22]. A recent systematic review of polysomnographic findings confirmed decreased sleep efficiency, slow wave sleep and rapid eye movement sleep along with increased wake time after sleep onset in people with HD when compared to healthy controls[23]. Wrist worn devices have been used in clinical studies to assess inactivity-activity patterns in HD[24]. Caution is however required when applying standard algorithms (not validated in HD) in populations

where involuntary movements may limit inferences[25]. Although not previously investigated in HD, there is support from the sleep disorder literature that regular physical activity (including the development of routines) may be an important factor in management of sleep disturbance[26] and that management of sleep-related symptoms has a positive impact on quality of life in patients with neurodegenerative disorders[27].

4.4 Diet and HD

The largest study to date of dietary factors involved participants in the *Prospective Huntington At Risk Observational Study* (*PHAROS*) in which 1001 participants were enrolled and followed up every 9 months between 1999 and 2010. A sample of PHAROS participants (n=435) completed a semi-quantitative food frequency questionnaire that was used alongside clinical data in relation to HD symptoms[28]. Higher caloric intake was related to both higher CAG repeat length and higher five-year probability of onset of HD after adjustment for relevant covariates. Further investigation of a sub-set of the PHAROS cohort revealed no association between a Mediterranean Diet and age of onset of HD[29]. However higher consumption of dairy products was associated with increased risk of phenoconversion or onset of the disease. Interestingly, moderate adherence to a Mediterranean diet was associated with better quality of life, lower comorbidity, lower motor impairment and lower risk for abdominal obesity in a cohort of 98 Spanish HD participants[30]. In another study, families were interviewed in detail about their socio-economic (housing, education), eating (milk, cheese, fish), drinking (coffee, alcohol) and smoking habits and this information was considered in relation to their age of onset and course of disease. No relationships were identified for any of the reported factors aside from milk intake and the authors critically discuss this finding as very likely being a type I error[31]. On the contrary, caffeine intake (>190mg/day ~2 cups of coffee) assessed through the completion of a retrospective dietary survey in 80 HD participants (adjusted for sex, smoking status and CAG repeat length) was associated with earlier symptom onset[32]. The methods of data collection (i.e. retrospective self-reported recall) and the natural bias introduced by observational data make it very difficult to draw firm conclusions as to the role of diet in HD onset and progression. The only published randomized controlled evaluation[33] of a dietary supplement (namely co-enzyme Q10) found no effect for the use of this particular supplement. However, this may be due to the focus on a particular aspect of the diet as opposed the overall dietary pattern which is now recognised as being more important.

While the aforementioned studies report associations between AAO and/or progression of HD in relation to lifestyle passivity and diet, the broader application of results from these studies has remained challenging due to the unmeasured confounding caused by disease attributes (for example CAG length) that yield potentially meaningful imbalances between individuals from different subgroups of interest. These prior studies used multiple linear regression models to examine associations, without careful consideration of potential imbalances that might exist between individuals within the groups being compared (e.g. those with passive vs active lifestyles). The use of multiple regression models limits definitive conclusions with respect to causality. Additionally, AAO is known to be an inaccurate measure of disease onset for HD positive individuals[34]. Finally, and most critically, the aforementioned studies lack detailed and valid measures for many of the factors of interest (not least physical activity). Advances in technology and an ever-growing demand for wearable activity monitoring devices has resulted in a wealth of commercially available products with ever expanding capabilities. Such advancements mean that minimally invasive, low power, user

friendly devices are becoming more prevalent on the consumer market. However, products are yet to specifically target the collection of data on individuals with movement disorders, instead using algorithms trained on healthy control data that do not account for varied movement patterns seen in individuals with a given condition.

Currently, a key barrier to successfully exploring the impact of several promising manipulations of lifestyle elements is our limited ability to precisely measure, visualise and influence a given individual's 'real life' exposure to modifiable factors. The Enroll-HD study is a global observational study of people with HD where longitudinal clinical research data is collected, but at this time this comprehensive repository of prospectively collected research data does not have the capacity to incorporate the digital, sensor-based approaches that are essential for the efficient and person-centred assessment of physical activity, sleep and dietary intake. Therefore, in this study we plan to develop a contemporary digital and sensor-based approach to support the naturalistic assessment of physical activity, sleep and dietary intake to supplement this already established international cohort of individuals with HD.

4.5 Rationale for current Study

The hypothesis underpinning this study is that we can influence prognosis in HD through the use of digital technology as a naturalistic, 'real world' approach to symptom detection and environmental modification[35].

Our specific research questions are:

1. How do physical activity, sleep, dietary intake and identified genetic modifiers inform disease outcomes over 12-months?
2. What are the essential requirements of a multi-modal life-style intervention where visualisation of naturalistic patient generated data derived through digital, sensor-based assessment is likely to be a key feature?

5 Study objectives/endpoints and outcome measures

5.1 Primary objectives

Establish the feasibility of linking lifestyle factors, with genetic risk factors to explore their interplay with HD symptom severity.

5.2 Secondary objectives

i. Establish feasibility and acceptability of using digital technologies to consistently collect information directly from people with HD about their physical activity, sleep and diet.

ii. Evaluate how appropriate commercially available activity trackers are to measure physical activity and sleep in people with HD.

iii. Design lifestyle and / or behavioural interventions aimed at improving the quality of life of people with HD.

5.3 Exploratory objectives

Exploratory objectives are associated with each Phase 1 sub-study outlined in Appendix A. Study design and setting

6 Study Design and Setting

DOMINO-HD is a consortium led observational study of behaviour and lifestyle in people with early-to-mid stage HD. This protocol focuses solely on the research being undertaken in [site specific details] as part of this consortium and as part of the Phase 2 observational study.

This protocol involves the longitudinal data collection of physical activity, sleep and dietary intake data in up to 120 participants (minimum 60) with HD in [site specific details]. We will recruit participants from current Enroll-HD sites over a period of 10 months, with a follow-up period of 12 months. 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. Upon recruitment into the study, baseline DOMINO-HD measures will be collected in addition to the routine annual Enroll-HD visit. Participants will then be provided with a commercially available physical activity monitor to take home for continuous data collection for the follow-up period. During this time, participants may be asked to complete an additional 7 day/night activity assessment in the home involving additional wearable sensors to track their physical activity and sleep. Measures of disease progression will be captured at 12 months via the next annual Enroll-HD visit, with the option of completing additional DOMINO-HD clinical assessments

6.1 Risk assessment

A study risk assessment has been completed to identify the potential hazards associated with the Phase 2 clinical study being performed across all participating clinical sites and to assess the likelihood of those hazards occurring and resulting in harm. The risk assessment 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 12-month clinical observation study has been categorised as a low risk, where the level of risk is comparable to the risk of standard medical care. A copy of the study risk assessment may be requested from the study manager. The study risk assessment is used to determine the intensity and focus of monitoring activity.

7 Site and Investigator selection

This study will be carried out at a participating Enroll-HD site in Europe that is currently run or attended by DOMINO-HD consortium partners. Before the site can begin recruitment, a Principal Investigator at the site must be identified (it is expected that this will be the consortium partner lead for a given location). The following documents must be in place and copies sent to the DOMINO-HD study email account (see contact details on page 4) prior to any recruitment taking place:

- 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. This may be limited to a favourable opinion from the host organisations Institutional Review Board, or may include further local permissions in addition to country specific ethical approval.
- Current Curriculum Vitae and GCP training certificate of the Principal Investigator (PI).
- GCP training certificate for all delegated researchers working in clinical settings.
- 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 (PIS) and Consent Form (ICF) on host care organisation headed paper.

Upon receipt of all the above documents, the Study Manager will send written confirmation to the PI confirming that participant recruitment can begin. This letter/email must be filed in the Investigator Site File (ISF). Along with the written confirmation, a study pack will be produced, holding all the documents required to recruit into the study.

The DOMINO-HD consortium lead, Cardiff, will provide [specific site name] with a copy of the master protocol and a template for the participant information sheets and informed consent forms which can be adapted to local needs as required. Any changes to the master protocol will be circulated to sites by the coordinating centre, with responsibility remaining for individual sites to obtain local approvals. Any site training deemed necessary will be performed remotely via videoconferencing.

8 Participant selection

Participants are eligible for the study if they meet all the following inclusion criteria and if none of the exclusion criteria apply. All queries about participant eligibility should be directed to the Study Manager before registration. Whilst it would be preferable for participants to be accompanied to assessments by a friend or relative, we will not exclude potential participants who are unable to attend with a partner.

8.1 Inclusion criteria

- Diagnosis of HD confirmed by genetic testing.
- Above the age of 18.
- Diagnostic confidence level (DCL) 3 and 4 (which can include both pre-motor [late prodromal] or motor manifest HD.
- Self-ambulatory.
- A participant (current or newly enrolled) in the Enroll-HD study (with a preference for those who have been genotyped in GWAS3-5 or are to be genotyped in GWAS6).

8.2 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.
- Severe medical conditions such as unstable or progressive heart disease, uncontrolled diabetes, severe liver, kidney or thyroid dysfunction or similar medical conditions.
- Any acute or unstable psychiatric conditions.
- Unable to tolerate long-term wear of an activity monitor.
- Inability or unwillingness of participant to give written informed consent.
- No access to a smartphone.
- Not willing to install, or allow the research team to install Apps on their smartphone related to the study.

9 Recruitment, Screening and registration

9.1 Participant identification

Participants will be identified from the Enroll-HD database at the [site specific details] Clinical Site. Enroll-HD monitors the onset of the disease and its progression in different people and is open to the following categories: gene carriers, gene negative and family controls. Information on potentially eligible participants (along with race, age, gender and BMI) will be provided to sites from the central Enroll-HD study teams following Enroll-HD standard operating procedures.

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 and genetic data are shared with the researchers therefore, the risk that identifying information will be accidentally disclosed is low.

Records of participants registered on Enroll-HD at the [site specific details] clinical site will be reviewed centrally by Enroll-HD staff for potential eligibility according to the stated inclusion criteria. Local site staff will then use the lists generated to target recruitment after more detailed review for eligibility. Those that fit the inclusion criteria and none of the exclusion criteria will be sent an invitation to participate in DOMINO-HD 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 study and discuss their potential involvement before providing informed consent. If an individual attends the [site specific details] Clinical Site and is deemed suitable for inclusion in DOMINO-HD but is not an Enroll-HD participant, it will be acceptable to co-recruit them to Enroll-HD and DOMINO-HD at the same time. All DOMINO-HD participants must also be part of Enroll-HD due to the data linkage explained later in this protocol and therefore is listed as an inclusion criterion for this study.

9.2 Screening logs

A log of all potentially eligible participants (as defined by the study inclusion criteria) will be maintained at the [site specific details] Clinical Site. 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 screening (as they met any of the study exclusion criteria) or were enrolled in the study. 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 dominohd@cardiff.ac.uk monthly. All pre-screening (conducted as part of the process of participant identification) and screening information will be recorded centrally to inform STROBE compliant reporting of participant enrolment, follow up and analyses.

9.3 Recruitment

Up to 120 participants (minimum 60) will be recruited in [site specific details] under this protocol.

9.4 Informed consent

Once potential participants have received the study information, talked to family members and/or caregivers, and clarified any questions, informed consent will be obtained. Consent may be taken by qualified researchers or clinicians, details of which will be recorded on the delegation log at the site. Only when written informed consent has been obtained from the participant and they have been enrolled into the study can they be considered a study participant. Participants should always be asked to sign a consent form before conducting any study mandated procedures. One copy should be given to the participant, but the original copy should be kept in the Investigator Site File at the clinical site. The right of the subject to refuse to participate in the study without giving reasons must be respected. Similarly, the participant must remain free to withdraw at any time from the protocol without giving reasons and without prejudicing their further treatment.

9.5 Registration

Potential participants will be screened for eligibility by local site teams after central Enroll-HD pre-screening as described in section 9.1. Those meeting eligibility criteria and providing informed consent will be registered as a study participant and assigned a unique study identification number prior to baseline data collection.

10 Withdrawal & lost to follow-up

10.1 Withdrawal

Participants have the right to withdraw consent for participation in any aspect of the study at any time. The participant's ongoing care will not be affected by a decision to withdraw from the study.
If a participant initially consents but subsequently withdraws from the study, clear distinction must be made as to what aspect of the study the participant is withdrawing from. These aspects could be:

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

The withdrawal of participant consent shall not affect the study activities already carried out and the use of data collected prior to participant withdrawal, unless specifically stated by the participant. In all instances participants who consent and subsequently withdraw should complete a withdrawal form or the withdrawal eCRF in the study 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 will be sent to dominohd@cardiff.ac.uk. Any queries relating to potential withdrawal of a participant should be forwarded by email to: dominohd@cardiff.ac.uk.

10.2 Lost to follow up

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. We will adhere to the Enroll-HD protocol for managing lost to follow up participants. This means that a participant will be deemed as lost to follow up if they do not attend the 12-month assessment, within a period of 8 weeks of the scheduled assessment.

If a participant is deemed to be 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 unless they are lost to follow up in the Enroll-HD study. We will consider the use of attrition weights to help ensure our sample with follow-up data is representative of the group of participants who originally enrolled in the study.

During the 12-month observational phase, participants will be prompted to wear their Fitbit and sync their data with the App for upload. The type of prompts will be the subject of a trial within a study (TWAS) which is documented separately, but as part of this, failure of the participant to provide less than 50% of expected data over a 4 week period will trigger a phone call from the research team. This will serve two purposes; see if the participant requires help with using and syncing the device and to determine if the participant want to continue in the study.

11 Study procedures

11.1 Recruitment and follow-up

A maximum of 120 (minimum of 60) people with HD in [site specific details] will be recruited to this longitudinal observational study. Participants taking part will be in the study for approximately 12 months.

11.2 Assessments

This is an observational study where physical activity, sleep and diet will be monitored using a combination of wearable devices and questionnaires over a 12-month period. Participants will undergo baseline and optional 12-month follow up clinical assessments at [insert site specific details] with an enriched 7 day/night in-home monitoring assessment using additional measuring devices. All

DOMINO-HD participants will be involved in the Enroll-HD study which will allow access to additional clinical assessment data for all DOMINO-HD participants. Each element of this protocol is described below.

12-month observational study:

All participants will be given a single activity tracker (FitBit Charge 4) at their baseline visit which they will be asked to wear on their non-dominant wrist for a 12-month period. This tracker uses information from the on-board accelerometer, gyroscope/altmeter and heart rate sensor to estimate summary daily metrics for physical activity (such as step counts in minutes, hours and day granularity, number of floors climbed, intensity of activity performed), sleep (such as total minutes asleep and time spent in different sleep stages) and heart rate. Site staff will provide initial help with the installation and synchronisation of this wearable device to the participant's smart phone, including the installation and sign up to proprietary third party Apps and/or those developed in-house by the DOMINO-HD consortium to facilitate streamlined data transfer. Demonstrations, instructions and practical manuals will be provided for participants to take home to act as a troubleshooting guide and will include details on the charging method and how to transfer data from their device to the digital database platform. At time of consent, participants will agree to their personal and activity tracker data being stored in a third party cloud based platform which will be accessed by the research Team at Cardiff and a software developer subcontractor. We will take steps to pseudonymise the data by ensuring that all accounts and e-mail addresses used to upload data do not feature any identifiable personal data and will only be identified using the participants study identification number.

At any time during the 12-month observational study, participants may also be asked to complete a detailed 7 day/night assessment of their physical activity and sleep. This will provide supplementary raw data from a range of sensors which can be used to develop greater insight into the physical activity and sleep patterns in people with HD. An overview of the sensors and assessments required during this 7 day / night period are outlined in Table 1. Participants will be asked to visit the <insert site details here> where they will be given a range of devices to take home which will need to be worn for 7 days and 7 nights to complete a free-living physical activity and sleep assessment during their normal home routine. This will include up to three activity monitoring devices worn simultaneously (with two on the wrist and one on the thigh). Participants will be given detailed and simplified demonstrations of how to interact with each device. Paper documents will also be given to every participant explaining what to do if they have any problems with a device, how to contact the research team and a list of how to solve common problems with each device that they take home. Most devices require very little operation from the participant with limited charging required during the week long period. The participant either logs the data until the device is returned to the research team or uses an easy synchronisation procedure with a mobile phone app.

Participants will also be asked to complete electronic diaries (with paper backups) and questionnaires related to activity level, and sleep so that comparisons can be made between the data provided by the devices and the participant's perception of their activity and sleep for the week.

Following the 7 days/nights, participants will be asked to return the devices to the researcher by visiting the clinic or sending via a pre-arranged courier service. Participants will only return the

supplementary sensors and will continue wearing the original wrist worn activity tracker (Fitbit) for the remainder of the 12-month study. Data from devices with on-board data logging will involve manual download of data by the research or clinical team using third party proprietary software. Devices with cloud data synchronisation will have automatically uploaded their data to the cloud using third party methods on the device and mobile phone/tablet. This data will be accessed by the research or clinical team so that a local copy of the data can be stored. All downloaded data will be stored securely locally at [site specific name] and on a dedicated Cardiff University server who are the central data coordinators across the DOMINO-HD partner sites. When returning the devices, participants will be asked about their experience of using the devices, through completion of a user evaluation and comfort questionnaire.

Table 1. Overview of the 7-day, 7-night in-home physical activity and sleep assessment.

Measure	Time to complete	Frequency of collection	Location of collection
7-day monitoring of free-living physical activity wearing the standard 12-month monitoring device (Fitbit) along with an additional wrist (Actigraph) and thigh (ActivPal) activity tracker.	As many waking hours as possible	Daily for 7 days	Participants home
Daily physical activity and sleep diary to be completed on paper forms to be returned to the clinical site at the end of the week assessment or completed electronically.	15 min	Daily during the monitoring period	Participants home
Sleep Questionnaire for Huntington's Disease completed on paper or eCRF.	10 min	Once at end of 1-week monitoring period	When returning devices or remotely via telephone, electronic forms or returning paper forms in the mail.
International Physical Activity Questionnaire (IPAQ) (Short Form).	5 min		
7-day Physical Activity Recall (PAR) semi-structured interview.	20 min		
User evaluation of devices.	10 mins		
Comfort questionnaire	5 mins		

Given the digital nature of this data collection process, participants will be reminded to complete the required data syncing, surveys and diaries using automated digital prompts and latterly phone calls. This will be required specifically if excessive non-wear time is detected. The aim is to encourage participants to wear the device again and allow the research team to ascertain why the participant is not wearing the activity monitor. There is scant evidence available to determine the optimum frequency for prompting participants, therefore we will be running a TWAS in a bid to gather this evidence. In the TWAS, participants at site will be randomised to receive prompts at a routine frequency or in response to non-upload of data. The protocol for the TWAS will be documented separately.

At the end of the 12 months, participants will be asked to bring their 12-month monitoring device to the study team during their final follow-up clinical assessment for final data download and to gather views on usability and acceptability. Following this, the participant will be able to keep the Fitbit device and will not be asked to return it.

Baseline and 12-month DOMINO-HD clinical assessments:

Clinical assessments will be performed at Baseline and with the option of completing DOMINO-HD specific assessments at 12-month follow-up to supplement the observational physical activity, sleep and diet data collected in the home over 12-months. The assessments to be performed are described in Table 2.

Table 2. DOMINO-HD Phase 2 clinical assessments completed in clinic at baseline and 12-month follow up.

Construct	Measure	Time to complete	Baseline	12 Month Follow up
Patient-reported clinical symptoms	HD Pro-Triad: A patient reported instrument for the disease specific symptoms of HD including cognitive decline, emotional/behavioural dyscontrol and motor dysfunction.	10 min	✓	Optional
Nutrition assessment	European Prospective Investigation into Cancer and nutrition Food Frequency Questionnaire (EPIC-Norfolk FFQ): calculates nutrient and food group data from food frequency questionnaires.	30 - 60 mins	✓	Optional
	Malnutrition Universal Screening Tool (MUST): a 5-step screening tool to identify adults who are malnourished, at risk of malnutrition or obese.	10 min	✓	×
	EAT-10: A Swallowing Screening Tool: helps to measure swallowing difficulties.	10 min	✓	×
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 place into a purpose developed box is recorded. The addition of cognitive load increases the task complexity. Participants wear accelerometers on both wrists whilst undergoing the test.	15 min	Optional	Optional
Speech assessment	Perform sustained vowel sounds and the 51-item oral word reading test recommended by the American Speech-Language-Hearing Association expert panel.	10 mins	✓	×
Apathy assessment	Apathy Evaluation Scale Clinician: Test to quantify and characterise apathy based on clinician observation and subjects' self-reports during an interview.	10 mins	✓	×
Physical activity and mental activity and sleep assessment	Brunel Lifestyle Physical Activity Questionnaire self-report instrument that measures the planned and unplanned dimensions of lifestyle physical activity.	5 min	✓	Optional
	Lifetime of Experiences Questionnaire*‡	5 min	Optional	×
	The Lifetime Total Physical Activity Questionnaire‡.	5 min	✓	×
	Sleep Questionnaire for Huntington's Disease.	10 min	✓	Optional
	International Physical Activity Questionnaire (Short Form) will be used to assess 7-day physical activity, and to validate with the physical activity monitors.	5 min	✓	Optional
Anthropometrics	Body Mass Index, calf circumference and waist circumference:	5 min	✓	×

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Relationships assessment*	Relationship questionnaire. The Social Relationships questionnaire has been developed to assess quality of everyday relationships of HD patients by exploring how subjects judge their own relationship quality through their experiences of social interaction, and not only the relationship deterioration. The scale composed of a set of 49 items assessed on a 6-point Likert scale (from -3 to +3: Absolutely true, True, Mostly true, Mostly false, False, Absolutely False).	10 min	✓	×

~~* Denotes optional assessment ‡ Denotes baseline only assessment~~

Linked Enroll-HD data:

All DOMINO-HD participants will also be involved in the Enroll-HD study which involves annual clinical assessments (the full Enroll-HD protocol can be found at https://www.enroll-hd.org/enrollhd_documents/Enroll-HD-Protocol-1.0.pdf). DOMINO-HD assessments will be linked to the relevant visit based Enroll-HD data using an established linkage process. We will obtain these data via an approved specific data request as detailed in Appendix B. All DOMINO-HD 12-month follow up assessments will coincide with the annual ENROLL-HD visit ± 8 weeks).

11.3 Follow-up

The follow-up period for this observational study is 12 months. The baseline and 12-month assessment time points are designed to coincide with the participant's annual Enroll-HD assessment (± 8 weeks).

12 Safety reporting

This study is an observational study where participants are providing data but are not receiving an intervention of any kind. We do not therefore anticipate any intervention related adverse events (AE). There may however be instances of adverse events related to protocol mandated activities in the clinic (e.g. falls that may occur during clinical assessments and skin reactions as a result of wearing devices).

Adverse events will be documented following local protocols and subject to formal local reporting procedures if deemed to be serious.

We will not monitor AE or SAE outside of the face to face assessments at baseline and 12 months. The local Principal Investigator is responsible for ensuring that all site staff involved in this Study 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 Study team in Cardiff who are the DOMINO-HD coordinating site unless the SAE is specified as not requiring immediate reporting.

As part of the clinical assessment at baseline and 12 months, participants will be asked to complete the EAT-10 and MUST questionnaires. These tools have the potential to uncover medical problems that require ongoing treatment.

The local site PI should be consulted immediately should any participant score a 2 (high risk) on the MUST or 3 (moderate problem) or above on the EAT-10 and local policy should be implemented as

appropriate. For participants assessed as high risk on the MUST, the PI should consider onward referral to a dietician or nutritional support team.

If participants receive a score of 1 on the MUST, guidelines suggest documenting dietary intake for 3 days. If this is adequate the participant should be screened for malnutrition in another 2-3 months. If inadequate, local policy should be followed (consult with PI) and goals set to improve and increase overall nutritional intake.

Data regarding EAT-10 and MUST scores will be recorded in the study database. Sites should notify the coordinating site of any incidence where EAT-10 or MUST scores are a cause for concern in any participant, but these do not need to be reported specifically as adverse events.

12.1 Definition

Table 3. Safety reporting definitions.

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant or clinical Study participant administered an intervention 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 Study 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 subjects 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.

12.2 Causality

The Chief Investigator will assess each SAE to determine the causal relationship.

Table 4. Determining causality

Relationship	Description	Reasonable possibility that the SAE may have been caused by protocol mandated activities?

Unrelated	There is no evidence of any causal relationship with the intervention	No
Unlikely	There is little evidence to suggest there is a causal relationship with the intervention (e.g. the event did not occur within a reasonable time after administration of the Study 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 intervention (e.g. because the event occurs within a reasonable time after administration of the Study 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.

12.3 Expectedness

The assessment of whether or not an SAE is an expected consequence of taking part in the study will be provided by the Chief Investigator. Depending on the nature of the event, the reporting procedures outlined in this protocol should be followed. Any queries concerning adverse event reporting should be directed to the Study Manager.

12.4 Reporting procedures

12.4.1 Participating Site Responsibilities

The PI (or delegated appropriately qualified doctor from the study team) should complete the relevant AE or SAE CRF. Investigators should also report SAEs to their own health institution or IRB in accordance with local practice.

A completed SAE form for all events requiring immediate reporting should be submitted via the study database or emailed to the co-ordinating centre within 24 hours of knowledge of the event. A separate form must be used to report each event, irrespective of whether the events had the same date of onset. The participant will be identified only by study PID. The participant's name should not be used on any correspondence.

Serious Adverse Event (SAE) email address:

dominohd@cardiff.ac.uk

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.
Participating sites should adhere to their own local reporting procedures for SAEs.

SAEs should be reported if they occur during face to face assessments at baseline and 12-month follow up. SAEs do not need to be reported if they occur outside of these assessment visits.

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

- Full participant Study number
- An Adverse Event
- A completed assessment of the seriousness, and causality as performed by the PI (or another appropriately medically qualified doctor 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 on the CRF following the CRF procedure described in Section 16.

12.4.2 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 last participant completes their follow up assessment.

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. There is no requirement for annual safety reports in addition to the information provided through the annual progress report.

13 Statistical considerations

13.1 Sample size

The most well-known prospective observational study of predictors of progression, not including environmental factors, recruited 366 participants of which 345 completed 12-month follow up. We will recruit 300 participants from 5 clinical sites, making this one of the largest longitudinal studies of environmental risk factors on progression in HD[36]. Our prior work in similar sized clinical sites, recruiting to studies with comparable assessments and burden to participants guided the decision of a sample size of 300. In our experience, a recruitment target of approximately 60 participants per

clinical site is feasible and realistically achievable in the given time period. This sample size was then used to estimate the degree of power that could be achieved in the analysis with the available data. When modelling our environmental measures as continuous predictors in our regression models, the minimum effect size (ES) reported represents the minimum change that would be detected as statistically significant with 80% power for a 1-unit change in the environmental measure: this is clinically meaningful. Our detailed phenotyping will greatly enhance the power to detect effects (including genetic) and with a target recruitment of 300, we expect 80% power to detect a minimum ES of at least 0.23 at nominal significance (p=0.05), suggesting the study has reasonable power for small to moderate effects. Given the exploratory nature of this study, multiple testing correction will not be applied.

13.2 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. In the case of a substantial amount of missing data (>5%) the underlying mechanism of missingness (e.g. missing-at-random) will be investigated and missing data imputed using techniques such as multiple imputation by chained equations (MICE).

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

A statistical analysis plan (SAP) will be developed over the course of the study. Any subsequent deviations from this plan will be submitted as substantial amendments where applicable and recorded in subsequent versions of the protocol and SAP.

13.4 Termination of the Study

Termination criteria are not required for this study. This is a low risk observational study. The study as a whole will only be discontinued prior to the collection of all data if there is an unacceptable SAE event rate and a decision is made by the Study Management Group.

13.5 Inclusion in analysis

All participants enrolled into the relevant longitudinal cohort study (Phase 2) by all partners will be included in the analysis of the cohort study results unless they specifically request to withdraw their data from analyses.

14 Analysis

14.1 Analysis of 12-month longitudinal assessment data

1) Physical activity data: Data from the activity tracker will be collated with activity diaries and questionnaires for all of Phase 2 participants across all clinical sites to provide a summary overview of physical activity across the cohort.
2) Diet data: Information from the EPIC-FFQ will be collated across the cohort to produce a summary overview of nutrition.
3) Sleep data: Sleep data obtained from activity trackers worn and sleep diaries and questionnaires will be collated to generate a summary overview.
4) Device acceptability: summary data from user evaluations will be generated.

Activity and sleep metrics provided by the wearable devices will be examined, and summary statistics (e.g. mean, standard deviation, median, quartiles) will be reported for each metric. Unsupervised machine learning methods will be investigated to identify clusters (such as groups with distinct physical activity patterns) within the cohort. Supervised machine learning methods will be used together with feature selection to identify sleep and activity metrics which may be useful to predict disease progression. Appropriate cross-validation and validation methods will be implemented in the development of machine learning models. Methods to visually represent daily/weekly/monthly physical activity and sleep patterns will also be implemented.

14.1.1 Calculation and derivation of Composite measure of HD severity/progression

For calculation of the clinical composite score, we plan to use the composite UHDRS (cUHDRS) to provide us with a global measure of HD clinical symptoms and progression derived by Schobel et. al. [37] as follows:

$$cUHDRS = \left[\left(\frac{TFC - 10.4}{1.9}\right) - \left(\frac{TMS - 29.7}{14.9}\right) + \left(\frac{SDMT - 28.4}{11.3}\right) + \left(\frac{SWR - 66.1}{20.1}\right)\right] + 10$$

Composite behavioural scores will be derived based on the data emerging from WP1. They will be fully detailed in the formal statistical analyses plan and will likely include established measures in the relevant domains; for example, total step counts per day or time spent being active for the physical activity score. This may involve statistical techniques for dimensionality reduction such as principal component analysis.

14.1.2 Derivation of genetic liability measures

The GWAS data available for each DOMINO-HD participant will be used to derive polygenic measures[38] of genetic risk for relevant traits, including age at motor onset[6] and progression[3] in HD, psychiatric disorders (since these show genetic overlap[39] with psychiatric symptoms in HD, intelligence[40] and sleep)[41]. These will be tested for association with the progression measures, both directly and as interactions with the measures of physical activity, sleep and diet. They will also be used in analyses of causality (section 14.1.3).

14.1.3 Analyses of causality

Propensity score weighting methodology will be applied to robustly examine the causal effect relationship between our multi-domain environment measures and composite measures of HD severity and progression (14.1.1). These analyses will include the genetic risk measures (Section 14.1.2) to improve the accuracy of the weighting. The genetic risk measures will also be used to assess causal effects of the lifestyle measures on severity/progression using Mendelian randomisation approaches.

15 Data Management

Standard source data will be collected such as screening logs, informed consent, registration and incidence reporting (see Table 5). Additional data will be collected from a range of activity trackers,

self-reported questionnaires / surveys and clinical assessments, all of which are described below and summarised in Tables 6. Data will be centrally managed in DOMINO-HD databases.

All source data will be identified using the participant' study identifier (PID) and not with any personal identifiable information. The PID will be used to label all data files and paper CRFs.

Table 5. Standard study data collected.

Standard study data	**Screening log**	**Consent Form**	**DOMINO-HD database**	**Paper CRF**	**SAE form (as back up)**	**AE form (as a bask up)**
Pre-screening	X					
Eligibility screening	X					
Informed consent		X				
Registration			X	X		
Serious Adverse Events (clinic and motion analysis lab only)			X		X	
Adverse events (clinic and motion analysis lab only)			X			X
Participant withdrawal			X			

Table 6. List of study data to be recorded for Phase 2 and the location of that source data.

Phase 2 data: 12-month observational study	eCRF or paper CRF	C3t App and sensor software platform	Encrypted audio-recorder	FitBit Server	3rd Party proprietary software export	Enroll-HD data access request
HD Pro Triad	X					
EPIC-Norfolk FFQ	X					
Instrumented C3t		X				
Speech assessment			X			
Apathy Evaluation Scale	X					
Brunel Lifestyle Physical Activity questionnaire	X					
Sleep questionnaire for Huntington's disease	X					
Lifetime of Experiences Questionnaire	X					
The Lifetime Total Physical Activity Questionnaire.	X					
IPAQ (short)	X					
Self-reported activity and sleep diary	X					
Fitbit activity and sleep metrics				X		
User evaluation of devices	X					
Comfort questionnaire	X					
Malnutrition Universal Screening Tool (MUST)	X					
EAT-10	X					
Anthropometrics	X					
Relationship questionnaire	X					
In-home 7 day/night assessment (in addition to in-home longitudinal monitoring data)						
Actigraph watch					X	
ActivPal thigh sensor					X	
7 day PAR	X					
Data linkage						
Linked Enroll-HD data						X

Source Data is defined as *"All information in original records and certified copies of original records of clinical findings, observations or other activities in a clinical Study necessary for the reconstruction and evaluation of the Study. Source data are contained in source documents."* There is only one set of source data at any time for any data element, as defined in site source data agreement.

15.1 Collection of activity data from activity trackers.

Three devices may be used simultaneously or independently to collect physical activity and/or sleep data.

1) Fitbit wrist worn physical activity monitors will be used to obtain summary physical activity, heart rate and sleep data. Data will be uploaded from the device to the Fitbit server via a proprietary mobile device software application. Data uploaded to the Fitbit server will be identified using the study PID and not with any identifiable information to protect the participant's confidentiality. This will be achieved by using a study specific e-mail address for each participant which features their PID (to allow the correct identification of data streams by the study team) and does not require the use of personal e-mail addresses which may contain identifiable information. The Fitbit server will be accessed using the Fitbit Application Programming Interface via a third-party sub-contractor. Data collected as part of the Phase 2 clinical study will be accessed on a weekly basis by the CTR study team, with data being downloaded and stored locally on a regular basis. These devices have a watch face allowing participants to see information related to their physical activity and sleep but the information of interest to the study team cannot be modified.

2) Actigraph wrist worn physical activity monitors will be used to collect physical activity and sleep data. This will be collected during the 7 day/night free living assessments. Summary and raw accelerometer data gets uploaded from the device to the Actigraph software via a local computer connection on the day that the device is returned to the study team. All files will be identified using only the study PID and not with any identifiable personal information. These devices have a watch face allowing participants to see information related to their physical activity and sleep but the information of interest to the Study Team cannot be modified. The local site study team will be responsible for exporting data and transferring to the coordinating site via secure digital transfer.

3) ActivPAL thigh worn physical activity monitors will be used to collect physical activity and sleep data. This will be collected during the 7 day/night free living assessments. Summary and raw accelerometer data gets uploaded from the device to the ActivPAL software via a local computer connection on the day that the device is returned to the study team. As above, all files will be identified using only the study PID. These devices do not have a monitoring screen; therefore, participants have no means of accessing the data being recorded. The local site study team will be responsible for exporting data and transferring to the coordinating site via secure digital transfer.

All data rights and usage (for imported data) will be covered by the consortium agreement or relevant contractual arrangement. Details for the collection of source data via electronic and paper CRFs are detailed in section 15.4. Further detail on data management can be found in the DOMINO-HD Data Management Plan.

15.2 Collection of questionnaire and diary data

Participants will complete a range of questionnaires and diaries during Phase 2 data collections. These will be captured through paper and electronic CRFs.

15.3 Collection of clinical assessment data

A range of clinical assessments will be performed, each using their own data capture method. All will be collected electronically via i) a custom-built software collecting and saving data locally or to a CTR managed cloud database, ii) 3rd party proprietary software collecting and storing data either locally or to a cloud or iii) on a local encrypted audio-recorder. Participants will also be taking part in Enroll-HD where they will undergo additional annual clinical assessments. This data will not be collected by the DOMINO-HD research team, with the source data located within the Enroll-HD study. Access to this linked data will be obtained via a data access request which is detailed in Section 15.6.

15.4 Collection of personal data

Participants will be asked to provide local site staff with their mobile phone number to enable follow up of participants across the 12-month observational study. Individual sites will be asked to enter mobile phone numbers into the Essendex messaging platform for centralised management of the messaging service. Essendex stores information on an Amazon server that guarantees GDPR compliance and features and ISO certification for data security.

15.5 Completion of CRFs

The primary mode of data collection for DOMINO-HD will be via direct data entry into electronic CRFs via the individual researcher logins to the on-line study database. In Phase 2, for instances where access to the on-line database is not possible, a paper copy of each CRF will be provided in the Investigator 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.

15.5.1 Paper CRFs

Paper diaries/questionnaires for sleep and activity may be given to participants to complete as part of the 7 day and night free living assessment of activity monitors. Data from these CRFs will be entered into the main study database at a later date. All paper CRFs will be safely stored at site.

Paper versions of the electronic CRFs for Phase 2 will be made available in the Investigator Site File in the unlikely event that researchers at site are unable to access the DOMINO-HD database.

If a researcher is unable to upload the data into the DOMINO-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 as soon as is practicable and within at least one week of the data collection occurring. Any data captured in paper CRFs does not need to be returned to the central trial team but should be stored securely with the ISF at site.

15.5.2 Electronic CRFs

It is intended to develop data recording for this study as a web-based system. This is a secure encrypted system accessed by an institutional password and complies with the General Data Protection Regulation 2016. The system can be accessed on:

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

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:

- Registration
- 7 day self-reported physical activity and sleep diary
- User evaluation of devices.
- 7 day PAR semi-structured interview.
- HD Pro-Triad.
- EPIC-FFQ
- Brunel Lifestyle Physical Activity questionnaire.
- Sleep questionnaire for Huntington's Disease [42].
- Lifetime of Experiences Questionnaire.
- The Lifetime Total Physical Activity Questionnaire.
- IPAQ
- MUST
- EAT-10
- Anthropometric data entry form
- Relationship questionnaire
- Comfort questionnaire.
- SAE form
- AE form

All electronic CRFs should be completed in real time at the point of data collection. The CTR will send reminders for any overdue data. It is the site's responsibility to submit complete and accurate data in timely manner.

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. Data entered will be periodically monitored by the co-ordinating Cardiff team via validation and missing data reports. If missing or questionable data are identified, a data query will be raised and e-mailed to the participating site and the site will be requested to respond to that data query. The CTR will send reminders for any overdue data. It is the site's responsibility to submit complete and accurate data in timely manner. For further details on data management please refer to the DOMINO-HD data management plan.

15.6 Import of linked Enroll-HD data

All participants in DOMINO-HD will be participants in the Enroll-HD study and undergo annual clinical assessments as part of Enroll-HD. The DOMINO-HD study will make a specific data request to be approved by the Enroll-HD scientific planning committee to receive data exports from Enroll-HD for all DOMINO-HD participants (see Appendix B for details of data request). This will occur on a minimum of two occasions; 1) at the close of recruitment and 2) when the last participant has completed the 12-month follow up assessment. Data exports will contain coded datasets (using DOMINO-ID). Researchers in Cardiff will not be able to access the HDID (Enroll-HD identifier). Look up tables for

HDID to DOMINO-ID (PID) will be retained at the relevant site. Data exports will be imported into the DOMINO-HD database.

15.6.1 Genetic data linkage

Where possible, Phase 2 DOMINO-HD participants will have quality-controlled GWAS data as part of Enroll-HD. We will make a specific data request to the Enroll-HD scientific planning committee to receive these data (suitably anonymised – see Appendix C for details of data request). A secure, anonymised and robust data access strategy will be implemented in partnership with the data provider. GWAS genotype data will be stored in Cardiff (the central coordinating site) on a secure password-protected server. Summary data (e.g. genetic risk scores) will be shared with DOMINO-HD participating sites as required.

16 Protocol/GCP non-compliance

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

17 End of Study definition

This is an observational study, with the study end point defined as their last visit which will be the 12-month assessment performed in line with their annual Enroll-HD assessment.

18 Archiving

The SMF containing all essential documents will be archived at an approved external storage facility for a minimum of 15 years. The CTR will archive the SMF and SSFs 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.

19 Regulatory Considerations

19.1 Ethical and governance approval

This protocol forms part of a broader DOMINO-HD protocol that has approval from a Research Ethics Committee (REC) that is legally recognised by the United Kingdom Ethics Committee Authority for review and approval. Local governance approvals for each partner site are the responsibility of the local Principal Investigator.

19.2 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 General Data Protection Regulation 2016 following the Cardiff University information security framework and the

CTR General Data Protection Regulation policy. The data custodian and the translational sample custodian for this study is the Chief Investigator.

All data collection will be coded, with individual data sets identified by study identification number. No identifiable personal data will be collected in the DOMINO-HD study. Data shared between participating organisations will be done so pseudonymously and primarily via the study specific database.

All collected assessment data will be stored in the study specific database detailed in section 15.0. Raw activity monitor data will be held pseudonymously on a temporary basis within a software platform developed specifically for this data collection phase. For long term storage, activity monitor data will be transferred to a secure Network Attached Storage (NAS) drive as a Cardiff University hosted data storage modality. Summary metrics will stored within a Mongo database. At the end of the study, data exports from Enroll-HD and various physical activity summary data and questionnaire data will be linked into this database. 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 study 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).

19.3 Indemnity

Non-negligent harm: This study is an academic, investigator-led and designed study, 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 study and they cannot offer any indemnity.
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 Study (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.

19.4 Study sponsorship

Cardiff University will act as Sponsor for study. 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 study type. Responsibilities delegated to the CTR by sponsor can be found in the study delegation log and in the memorandum of understanding.

19.5 Funding

DOMINO-HD is a consortium study funded by the Joint Programme for Neurodegenerative Disorders. Each partner has been awarded their budget by local contributory funders within their country. These are individually managed at a local level. Support will be provided from the central coordinating team on individual site budgets and how they need to be spent. Individual partner funders are listed on cover page of this document.

20 Study management

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

20.1 SMG (Study Management Group)

The SMG will be convened to provide guidance on the running of the study and to act as a decision-making body for any issues that occur during the study. The SMG will consist of all consortium partner leads and project managers for each partner site, plus a Public and Patient Representative. SMG members will be required to sign up to the remit and conditions as set out in the SMG Charter. SMG meetings will occur monthly during the trial including set-up, analysis and close down. All meetings will be documented, and a record of the minutes will be held in the SMF.

20.2 Consortium Meetings

Consortium meetings will be held with all consortium partner leads and their respective teams to discuss study progress. These meetings will be held annually for the duration of the study and will always be held face-to-face.

21 Quality Control and Assurance

21.1 Monitoring

The clinical study risk assessment has been used to determine the intensity and focus of central monitoring in the DOMINO-HD study. There is no intention of performing any site monitoring as part of this study. Plans for central monitoring are fully documented in the study monitoring plan.
Investigators should agree to allow study 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 central monitoring will be shared with the Sponsor, CI, PI & local regulatory bodies.

22 Publication policy

All publications and presentations relating to the trial will be authorised by the Study Management Group and consortium partners as outlined in the consortium agreement and publication policy.
Authorship for presentations and publications will be decided by the SMG (all study 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 DOMINO-HD study publication policy.
In addition to journal publication, the results of the study will be fed back to participants via newsletter at the relevant participating sites.

23 Milestones

The GANTT chart will be monitored and updated monthly during SMG and stored in the eTMF.

24 References

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25 Appendices

Appendix A:

Phase 1 sub-studies performed as part of the broader DOMINO-HD project.

Sub-Study 1

DOMINO-HD sub-study title:	Validation of Fitbit Charge 3 physical activity metrics in Huntington's disease.
Study acronym:	SS1_physical_activity
Principal investigator:	Dr Philippa Jones (Cardiff University)
Co-investigators:	Cardiff University: Prof Monica Busse, Laura Mills, Vincent Poile University College Dublin: Dr Emer Doheny, Prof Madeleine Lowery
Planned sample size:	20
Planned clinical sites:	Cardiff University
Anticipated start date:	March 1 2020
Anticipated duration:	2 years
Inclusion criteria:	DOMINO-HD Phase 2 inclusion criteria
Exclusion criteria:	DOMINO-HD Phase 2 exclusion criteria
Description of Study:	
This study will explore the performance of the Fitbit charge 3 smartwatch as a physical activity monitoring device in people with Huntington's disease and the use of wrist and thigh worn accelerometers to describe physical activity characteristics in HD. This study will comprise of two parts. Firstly, people with HD will be invited to the motion analysis lab where they will perform a range of physical activities whilst wearing commercially available activity trackers and motion sensing devices. The measures provided by these devices will be analysed against the amount of activity each person actually performed to see how well they compare and whether the devices provide useful information about activity levels. Participants may also be asked to take some activity tracking devices home to collect free-living data and again assess the suitability of the devices for long term activity monitoring in HD. Having worn an activity tracker, participants will be asked to give feedback on how user-friendly the devices were and whether they were happy wearing them.	
Aim:	
Validate the performance of the Fitbit Charge 3 in monitoring physical activity in people with Huntington's disease.	
Objectives:	

1. Quantify the accuracy of physical activity and heart rate metrics provided by the Fitbit Charge 3 compared to ground truth information on number of steps performed whilst in the motion analysis lab setting. 2. Determine the influence that device location has on the quantification of physical activity metrics in people with HD. 3. Compare the physical activity metrics obtained from different devices worn on the wrist and thigh 4. Explore the movement signatures of people with HD performing physical activity/sleep using accelerometer devices in order to inform the development of HD specific activity trackers.

Sub-Study 2

DOMINO-HD sub-study title:	Development of novel objective clinical assessments in Huntington's Disease
Study acronym:	SS2_clinical_assessments
Principal investigator:	Prof Madeleine Lowery (University College Dublin)
Co-investigators:	University College Dublin: Vitoria Fahed, Dr Emer Doheny, Cardiff University: Prof Monica Busse, Dr Philippa Jones, Laura Mills and Anne Rosser
Planned sample size:	20
Planned clinical sites:	Cardiff University
Anticipated start date:	May 1 2020
Anticipated duration:	30 months
Inclusion criteria:	DOMINO-HD Phase 2 inclusion criteria
Exclusion criteria:	DOMINO-HD Phase 2 exclusion criteria
Description of Study:	
A number of recommendations have been made outlining a range of clinical assessments that should be performed by any research team investigating the progression of HD. Whilst this provides consistency across the research literature, it remains very challenging to sensitively measure the symptoms of HD. Additional sensitive, reliable and objective assessments that can take place in the clinical setting are vital in order to measure subtle changes in disease progression and to determine the success of therapeutic interventions. DOMINO-HD will develop new assessment methods that allow sensitive, objective assessments of HD symptoms. This will include the novel assessment of parameters believed to be clinically important: - Upper limb function will be measured using motion sensing devices (accelerometers) and sensors that measure muscle activity (electromyography). - Speech will be measured using audio-recordings and sensors that measure muscle activity (electromyography) and acceleration.	
Aim:	
Explore more sensitive and objective ways to assess the progress of HD within the clinical environment.	
Objectives:	
1. Investigate the ability to objectively measure motor symptoms in HD (namely chorea, dystonia and bradykinesia and speech abnormalities) using electromyography, accelerometer data and audio recordings.	

Sub-Study 3

DOMINO-HD sub-study title:	Validation of Fitbit Charge 3 sleep metrics in Huntington's disease.
Study acronym:	SS3_sleep
Principal investigator:	Prof. Dr. Hans Jung (HJ), University Hospital Zurich (USZ)
Co-investigators:	University Hospital Zurich: Prof. Dr. Christian Baumann University College Dublin: Dr. Emer Doheny (ED), Prof. Madeleine Lowery (ML), Cardiff University: Prof. Lesley Jones, Prof. Peter Holmans, Prof. Monica Busse, Dr. Philippa Jones, Vincent and Laura Mills
Planned sample size:	20
Planned clinical sites:	University Hospital Zurich
Anticipated start date:	March 1 2020
Anticipated duration:	3 years
Inclusion criteria:	DOMINO-HD Phase 2 inclusion criteria
Exclusion criteria:	DOMINO-HD Phase 2 exclusion criteria
Description of Study:	
This study will explore the performance of the Fitbit Charge 3 smartwatch as a sleep monitoring device in people with Huntington's disease (HD) and the use of the Sleeploop headband to describe sleep characteristics in HD. The study will comprise two parts: Firstly, the smartwatch will be compared to the gold standard for sleep monitoring, polysomnography (PSG), and the SleepLoop head-band, during an overnight sleep assessment in a supervised clinical environment. Secondly, the smartwatch sleep metrics will be compared to those reported by the head-band and also a self-reported diary and questionnaires related to sleep during an unsupervised seven-night in-home study. Specific characteristics of sleep in HD will be assessed in relation to PSG and Sleep Loop head band data.	
Aim:	
Validate the performance of the Fitbit Charge 3 in monitoring sleep stages in people with Huntington's disease against the gold standard for sleep assessment, PSG.	
Objectives:	
1. To quantify the accuracy of the sleep metrics provided by the Fitbit Charge 3 compared with the gold standard, polysomnography (PSG). 2. To quantify the accuracy of the sleep metrics provided by the SleepLoop compared with the gold standard, polysomnography (PSG), in HD. 3. To compare the performance of the Fitbit Charge 3 against the SleepLoop headband device during a seven night in-home study for assessing sleep-wake architecture and distinct behavioural states. 4. To understand the limitations of the Fitbit Charge 3 as a sleep monitor in Huntington Disease, and to develop methods to improve the accuracy of sleep metrics in this cohort. 5. To describe the sleep architecture of people diagnosed with Huntington Disease. 6. To investigate relationships between sleep metrics (as determined by PSG, SleepLoop and Fitbit Charge 3) and genetic biomarkers, assessed following DNA and RNA extraction. 7. To perform genetic analysis to examine possible associations of the genotype with sleep parameters 8. To analyse and disseminate results as appropriate. 9. To identify areas for future research based on study outcomes	

Sub-Study 4

DOMINO-HD sub-study title:	Investigating the impact of nutrition on disease progression and quality of life in those with Huntington's disease

Study acronym:	SS4_nutrition
Principal investigator:	Prof Esther Cubo (Hospital Universitario Burgos) & Prof Bernhard Landwehrmeyer (Ulm University)
Co-investigators:	Hospital Universitario Burgos: Carla Collazo Ulm University: Alzbeta Muehlbaeck, Jessica Rivadeneyra, Institute of Psychiatry and Neurology, Warsaw: Dr Grzegorz Witkowski University College Dublin: Prof Madeleine Lowery, Prof Lorraine Brennan
Planned sample size:	180
Planned clinical sites:	Hospital Universitario Burgos, Ulm University and Institute of Psychiatry and Neurology, Warsaw
Anticipated start date:	July 1st 2020
Anticipated duration:	30 months
Inclusion criteria:	DOMINO-HD Phase 2 inclusion criteria
Exclusion criteria:	DOMINO-HD Phase 2 exclusion criteria
Description of Study:	
This study will investigate the impact of nutrition on disease progression and quality of life in those with HD and forms a sub-study of the 12-month observational study being performed as part of DOMINO-HD. As standard, participants will undergo detailed clinical assessments at baseline (including a nutritional assessment via the Food frequency Questionnaire) before having their activity and behaviour monitored for 12-months using a Fitbit Charge 3 and then finally having a 12-month follow up of clinical assessments. This study will enhance the broader study by collecting additional nutrition information on a subset of 180 participants, focusing on those recruited in Burgos, Ulm and Poland. These additional measures include baseline blood samples to enable metabolomics analyses and a baseline Dexa Scan to enable the assessment of body composition and bone mineral density.	
Aim:	
Investigating the impact of nutrition on disease progression and quality of life in those with Huntington's disease	
Objectives:	
1. Determine the relationship between nutrition and the progression of HD. 2. Develop nutritional interventions aimed at improving the quality of life of people with HD.	

Sub-Study 5

DOMINO-HD sub-study title:	Validation of the Fitbit Charge 3 energy expenditure metrics in Huntington's disease.
Study acronym:	SS5_energy_expenditure
Principal investigator:	Prof Esther Cubo (Hospital Universitario Burgos) & Prof Bernhard Landwehrmeyer (Ulm University)
Co-investigators:	Hospital Universitario Burgos: Dr Alejandro Rodriguez, Carla Collazo Ulm University: Dr Alzbeta Muehlbaeck, Jessica Rivadeneyra, Cardiff University: Dr Philippa Jones. Prof Monica Busse University College Dublin: Dr Emer Doheny, Prof Madeleine Lowery
Planned sample size:	30 healthy controls and 30 people with HD
Planned clinical sites:	Hospital Universitario Burgos and Ulm University
Anticipated start date:	June 1st 2020
Anticipated duration:	12 months
Inclusion criteria:	DOMINO-HD Phase 2 inclusion criteria for HD cohort
Exclusion criteria:	DOMINO-HD Phase 2 exclusion criteria for HD cohort
Description of Study:	
This study will explore the performance of the Fitbit charge 3 smartwatch as a physical activity monitoring device in people with Huntington's disease (with specific focus on the ability estimate energy expenditure) and the use of wrist and thigh worn accelerometers to describe energy expenditure characteristics in HD. This study will comprise of two parts. Firstly, people with HD will be invited to the exercise laboratory where they will perform a range of physical activities whilst wearing commercially available activity trackers, motion sensing devices and equipment capable of providing gold standard measures of energy expenditure. Calories burnt, METs and activity intensity Fitbit Charge 3 metrics will be compared to the gold standard energy expenditure to determine whether these metrics are suitable when monitoring energy expenditure in HD. Participants may also be asked to take some activity tracking devices home to collect free-living data and again assess the suitability of the devices for long term activity monitoring in HD.	
Aim:	
Validate the performance of the Fitbit Charge 3 in monitoring energy expenditure in people with Huntington's disease.	
Objectives:	
1. Examine the accuracy of accelerometer based activity monitors which are frequently used in research to objectively quantify EE in free-living settings. 2. Examine the best anatomical location of the accelerometer to analyse EE. 3. Examine the energy expenditure (EE) for different activities. 4. Quantify EE, nutrition and its relationship with functional capacity in HD.	

Appendix B:
Specified Dataset Request Phase 2

The following variables from the core and extended battery data will be requested at baseline and follow up (12 months) for participants in Phase 2 via a specific data request to the Enroll-HD Scientific Review Committee.

Participant-Based Data Files (Enroll-HD PDS data dictionary)

Variables from Participant Profile
Gender (sex)*
Larger research CAG allele determined from DNA (caghigh)
Have motor symptoms compatible with HD ever been a part of the participant's medical history? (ccmtr)
At what age did the participant's motor symptoms begin? Age (years). (ccmtrage)
Can you, as a rater, estimate the time of symptom onset? (sxest)
Rater's estimate of symptom onset. (sxrater)
Confidence with which this estimation is made. (sxestcfd)
Rater's judgement of initial major symptom. (sxraterm)
Age of clinical HD diagnosis. (hddiagn)

Variables from "pharmacotx" (Pharmacotherapy)
Drug name – Modified Term (cmtrt__modify)
Ingredient – Modified Term (cmtrt__ing)
Ingredient – Code (coded by ATC) (cmtrt__atc)
Indication – Modified Term ((coded by MedDRA) (cmindc__modify)
Indication – Code (coded by MedDRA) (cmindc__decod)
Total daily dose (cmdostot)
Ongoing (**cmenrf**)

Variables from "nonpharmacotx" (Non-Pharmacologic Therapies)
Therapy (cmtrt)
Number of times (cmfrq)
Frequency (cmdosfrq)
Ongoing (cmenrf)

Variables from "nutsuppl" (Nutritional Supplements)
Type (cmcat)
NutSuppl Supplement – Modified Term (cmtrt__modify)
NutSuppl Supplement – Code (cmtrt__decod)
NutSuppl Supplement – ATC Code(s) (cmtrt__atc)
NutSuppl Supplement - ingredient(s) (cmtrt__ing)
Ongoing (cmenrf)

Variables from "comorbid" (Comorbid Conditions)
Condition – Modified Term (coded with ICD10) (mhterm__modify)
Condition – Code (coded with ICD10 + MedDRA) (mhx mhterm__decod)
Body system code (mhbodsy)
Ongoing (mhenrf)

Variables from "Clinical Trials"
Clinical trial name ctnm
Date of enrollment rfstdtc
What is ppt current clinical
trial status? ctstts
End date of participation rfendtc

Visit-Based Data Files (Enroll-HD PDS data dictionary)

Form "Variable Items"
Section General Variable Items I

Height (cm) (height)
Weight (kg) (weight)
BMI (bmi)

Does the participant currently drink alcohol? (alcab)
Units per week (alcunits)

Does the participant currently smoke? (tobab)
Packyears (packy)

Current caffeine use? (cafab)
Do you drink more than 3 cups of coffee, tea and cola drinks combined per day? (cafpd)
Does the participant currently use drugs? (drugab)

Group Drug use for non-medical reasons?
Group Marijuana
Abuse (mar)
Frequency (marfrq)

Section General Variable Items II
Marital status (maristat)
Residence (res)
ISCED education level (isced)
Employment (jobclas)

All Variables from UHDRS Motor table:
Motor score (TMS) (motscore)
Motor score (TMS) incomplete (miscore)

Group Ocular pursuit
Horizontal (ocularh)
Vertical (ocularv)

Group Saccade initiation
Horizontal (sacinith)
Vertical (sacinitv)

Group Saccade velocity
Horizontal (sacvelh)
Vertical (sacvelv)
Dysarthria (dysarth)
Tongue protrusion (tongue)

Group Finger taps
Right (fingtapr)
Left (fingtapl)

Group Pronate supinate-hands
Right (prosupr)
Left (prosupl)
Luria (luria)

Group Rigidity-arms
Right (rigarmr)
Left (rigarml)
Bradykinesiabody (brady)

Group Maximal dystonia
Trunk (dysttrnk)
RUE (dystrue)
LUE (dystlue)
RLE (dystrle)
LLE (dystlle)

Group Maximal chorea
Face (chorface)
BOL (chorbol)
Trunk (chortrnk)
RUE (chorrue)
LUE (chorlue)
RLE (chorrle)
LLE (chorlle)

Gait (gait)
Tandem walking (tandem)
Retropulsion pull test (retropls)
Diagnostic confidence level(DCL) (diagconf)

All Variables form UHDRS TFC table:
Functional score (tfcscore)
Occupation (occupant)
Finances (finances)
Domestic chores (chores)
ADL (adl)
Care level (carelevl)

All Variables form UHDRS Function table
Functional assessment score (fascore)
Functional score incomplete (fiscore)
Could subject engage in gainful employment in his/her accustomed work (emplusl)
Could subject engage in any kind of gainful employment? (emplany)
Could subject engage in any kind of volunteer or nongainful work? (volunt)
Could subject manage his/her finances (monthly) without any help? (fafinan)
Could subject shop for groceries without help? (grocery)
Could subject handle money as a purchaser in a simple cash (shop) transaction? (cash)
Could subject supervise children without help? (supchild)
Could subject operate an automobile safely and independently? (drive)
Could subject do his/her own housework without help? (housewrk)
Could subject do his/her own laundry (wash/dry) without help? (laundry)
Could participant prepare his/her own meals without help? (prepmeal)
Could subject use the telephone without help? (telephon)
Could subject take his/her own medications without help? (ownmeds)
Could subject feed himself/herself without help? (feedself)
Could subject dress himself/herself without help? (dress)
Could subject bathe himself/herself without help? (bathe)
Could subject use public transportation to get placeswithout help? (pubtrans)
Could subject walk to places in his/her neighbourhood without help? (walknbr)
Could subject walk without falling? (walkfall)
Could subject walk without help? (walkhelp)
Could subject comb hair without help? (comb)
Could subject transfer between chairs without help? (trnchair)
Could subject get in and out of bed without help? (bed)
Could subject use toilet/commode without help? (toilet)
Could subject's care still be provided at home? (carehome)
Subject's independence in % (indepscl)

Variables from Cognitive tables:
Section Core Cognitive Assessment
Symbol Digit Modality Test completed (sdmt)
Total correct (sdmt1)
Total errors (sdmt2)
Verbal Fluency Test (Category) completed (verfct)
Categorical Verbal Fluency (verfctd)
Total correct (1min) (verfct5)
Total intrusion errors (verfct6)
Total perseverative errors (verfct7)
Stroop Colour Naming Test completed (scnt)
Total correct (scnt1)
Total errors (scnt2)
Total self-corrected errors (scnt3)
Stroop Word Reading Test completed (swrt)
Total correct (swrt1)
Total errors (swrt2)
Total self-corrected (swrt3)

Section Extended Cognitive Assessments

Stroop Interference Test (sit)
Total correct (sit1)
Total errors (sit2)
Total self-corrected errors (sit3)

Trailmaking Test completed (trl)
Part A: time to complete (trla1)
Part A: total correct (trla2)
Part A: total errors (trla3)
Part B: time to complete (trlb1)
Part B: total correct (trlb2)
Part B: total errors (trlb3)

Verbal Fluency Test (Letters) (verflt)
Total correct (3 min) (verflt05)
Total intrusion error (verflt06)
Total perseverative errors (verflt07)

Variables from HADS-SIS table:
Anxiety subscore (anxscore)
Depression (hads_depscore)
Irritability subscore (irrscore)
Outward irritability subscore (outscore)
Inward irritability subscore (inwscore)

Variables from PBA-s table
Depression (depscore)
Irritability aggression (irascore)
Psychosis (psyscore)
Apathy (aptscore)
Executive function (exfscore)
For information only
depscore = sum of severity x frequency for depressed mood, suicidal ideation, anxiety
irscore = sum of severity x frequency for irritability and aggression
psych score = sum of severity x frequency for paranoid thinking, hallucinations apt score = severity x frequency for apathy
executive function exfscore = sum of severity x frequency for perseveration and obsessive compulsive behaviors.

Variables from SF-12 table
Physical Functioning (PF) (pf)
Role-Physical (RP) (rp)
Bodily Pain (BP) (bp)
General Health (GH) (gh)
Vitality (VT) (vt)
Social Functioning (SF) (sf)
Role-Emotional (RE) (re)
Mental Health (MH) (mh)
Physical Component (PCS) (pcs)
Mental Component (PCS) (mcs)

Appendix C:
Specified Dataset Request Phase 2

The following GWAS data will be requested for each recruited participant in Phase 2 via a specific data request to the Enroll-HD Scientific Review Committee:

1) a ".fam" file listing the IDs of the individuals, the relationships between them (for family data) and their disease phenotype
2) A "bim" file listing the SNPs and their chromosomal positions
3) A "bed" file containing the genotype calls – this is the largest file and typically in binary data (unreadable to humans)