

Enroll-HD Protocol  
Final Version 1.0  
09 September 2011



## **Enroll-HD:**

**A Prospective Registry Study in a Global Huntington's Disease Cohort  
A CHDI Foundation Project**

**Clinical Study Protocol  
Version 1.0  
09 September 2011**

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**Principal Investigator: G. Bernhard Landwehrmeyer, MD, PhD  
University of Ulm, Department of Neurology  
Oberer Eselsberg 45/1  
89081 Ulm  
Germany**



**Enroll-HD**

A Prospective Study in a Global Huntington's Disease Cohort

The final version of this Protocol has been approved by:

Christina Sampaio  
Christina Sampaio, MD  
Chief Clinical Officer, Enroll-HD

9/15/2011  
Date

G. Bernhard Landwehrmeyer  
G. Bernhard Landwehrmeyer, MD  
Principal Investigator, Enroll-HD

09/15/2011  
Date

**INVESTIGATOR OF RECORD SIGNATURE PAGE**

**Enroll-HD**

**Final Version 1.0, dated 09 September 2011**

A CHDI Foundation Project

I, the Investigator of Record, agree to conduct this study in full accordance with the provisions of this protocol. I will comply with all requirements regarding the obligations of investigators as outlined in the International Conference on Harmonization, Good Clinical Practices (GCP). I will also adhere to all local laws and regulations and as well as any applicable Safe Harbor privacy principles. I agree to maintain all study documentation.

I have read and understand the information in the study protocol and will ensure that all associates, colleagues, and employees assisting in the conduct of the study are informed about the obligations incurred by their contribution to the study.

\_\_\_\_\_  
Name of Investigator of Record

\_\_\_\_\_  
Signature of Investigator of Record

\_\_\_\_\_  
Date

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## **ABBREVIATIONS**

ACD	Acid Citrate Dextrose
COHORT	Cooperative Huntington Observational Research Trial
CRO	Contract Research Organization
CSRI	Client Services Receipt Inventory
CSSRS	Columbia Suicide Severity Rating Scale
DSMB	Data Safety Monitoring Board
eCRF	Electronic Case Report Form
HADS	Hospital Anxiety Depression Rating Scale
EDC	Electronic Data Capture
HD	Huntington's Disease
ICF	Informed Consent Form
ID	Identification
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MMSE	Mini Mental State Examination
PBA-s	Problem Behaviors Assessment-Short
REGISTRY-EHDN	REGISTRY – an observational study of the European Huntington-Disease Network
SF-12	Short Form Health Survey-12
SIS	Snaith Irritability Scale
SOP	Standard Operating Procedure
UHDRS	Unified Huntington's Disease Rating Scale
WPAI-SHP	Work Productivity and Activity Impairment-Specific Health Problem Questionnaire

## 1 SYNOPSIS

<b>Study Title</b>	Enroll-HD: A Prospective Registry Study in a Global Huntington Disease (HD) Cohort
<b>Study Design</b>	Observational, prospective, multi-national, multi-centre study without experimental treatment
<b>Funding</b>	CHDI Foundation, Inc., New York, USA
<b>Sponsor</b>	CHDI Foundation, Inc., or regional representatives of CHDI as designated by the Foundation
<b>Study Centers</b>	Sites in North America, Latin America, Europe, Asia, Australia and New Zealand.
<b>Study Period</b>	Enroll-HD is an open-ended, prospective study. Subjects will be asked to participate in as many annual study visits as possible.

<b>Study Objectives</b>	<p>Objective 1: To improve the understanding of the dynamic phenotypic spectrum and the disease mechanisms of HD by:</p> <ol style="list-style-type: none"><li>a. collecting natural history data covering the cognitive, behavioral and motor domains permitting estimates of rates of progression in HD and allowing insights into the neurobiology of HD,</li><li>b. collecting data and biologic samples to identify genetic and environmental factors influencing and/or modifying the HD phenotype and disease progression, and</li><li>c. promoting interrogatory studies that may provide clues to the pathogenesis of HD.</li></ol> <p>Objective 2: To promote the development of evidence-based guidelines to inform clinical decision making and improve health outcomes for the participant/family unit by:</p> <ol style="list-style-type: none"><li>a. assisting in the identification of beneficial interventions (clinical, pharmaco-therapeutic, non-pharmacologic),</li><li>b. facilitating the dissemination and implementation of currently proposed best clinical practices,</li><li>c. providing a platform for conducting outcome research, and</li><li>d. promoting exploratory data analysis projects that may identify processes to further improve the healthcare of affected individuals and their families.</li></ol> <p>Objective 3: To provide a platform to support the design and conduct of clinical trials by:</p> <ol style="list-style-type: none"><li>a. providing a resource to identify, develop and qualify novel assessment tools, clinical endpoints and biomarkers,</li><li>b. collecting longitudinal data to inform disease modeling studies, and</li><li>c. facilitating the identification of potential trial participants informing the selection of potential trial participants using data to estimate and quantify slopes/rates of disease progression (providing “run-in” data).</li></ol> <p>To achieve these objectives suitably de-identified and coded clinical information and biological samples collected from study participants will be made available to investigators for research purposes in accordance with procedures adopted by the steering committee.</p>
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<b>Study Population</b>	Subjects include individuals 18 years or older who are HD gene expansion mutation carriers independent of the phenotypical manifestation or the stage of HD and controls who do not carry the HD expansion mutation and who comprise the comparator study population. For individuals under the age of 18 years, those with clinically diagnosed features of HD in the setting of a confirmatory family history or a positive genetic test result may be included in this study.
<b>Number of Subjects</b>	This study aims to recruit all subjects who are eligible and willing to participate with a goal of enrolling approximately one-third of the HD affected population in each study region (North America, Latin America, Europe, Asia, and Australia/New Zealand).

<p><b>Inclusion Criteria</b></p>	<p>Individuals eligible to participate in Enroll-HD are classified into two major categories:</p> <ol style="list-style-type: none"> <li>1. <u>Carriers</u>: This group comprises the primary study population and consists of individuals who carry the HD gene expansion mutation.</li> <li>2. <u>Controls</u>: This group comprises the comparator study population and consists of individuals who do not carry the HD expansion mutation.</li> </ol> <p>These two major categories can be further subdivided into six different subgroups of eligible individuals:</p> <ol style="list-style-type: none"> <li>a. <u>Manifest/Motor-manifest HD</u>: Carriers with clinical features that are regarded in the opinion of the investigator as diagnostic of HD.</li> <li>b. <u>Pre-Manifest/-Motor-manifest HD</u>: Carriers without clinical features regarded as diagnostic of HD.</li> <li>c. <u>Genotype Unknown</u>: This group includes a first or second degree relative, i.e., related by blood to a carrier, who <u>has not undergone predictive testing for HD</u> and therefore has an undetermined carrier status.</li> <li>d. <u>Genotype Negative</u>: This group includes a first or second degree relative, i.e., related by blood to a carrier, who <u>has undergone predictive testing for HD</u> and is known not to carry the HD expansion mutation.</li> <li>e. <u>Family Control</u>: Family members or individuals not related by blood to carriers (e.g., spouses, partners, caregivers).</li> <li>f. <u>Community Controls</u>: Individuals unrelated to HD carriers who did not grow up in a family affected by HD. Data collected from community controls will be used for generation of normative data for sub-studies.</li> </ol> <p>Participant status will be captured in the study database using 2 variables: 1) <u>Investigator Determined Status</u>: this will be based on clinical signs and symptoms and genotyping performed as part of medical care, and will be updated at every visit and 2) <u>Research Genotyping Status</u>: this will be based on genotyping conducted as part of Enroll-HD study procedures. Based on research genotyping, participants will be reclassified under this variable from Genotype Unknown to 'Carriers' or 'Controls'. Investigators and participants will be blinded to this reclassification.</p>
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<p><b>Exclusion Criteria</b></p>	<ol style="list-style-type: none"> <li>1. Individuals who do not meet inclusion criteria,</li> <li>2. Individuals with choreic movement disorders in the context of a negative test for the HD gene mutation.</li> <li>3. For Community Controls: those individuals with a major central nervous system disorder will be excluded (e.g. stroke, Parkinson disease, Multiple Sclerosis, etc.).</li> </ol>
<p><b>Study Procedures</b></p>	<p>Enroll-HD is a prospective observational multicentre multi-national cohort study to be conducted in multiple native languages. Study visits will take place yearly and may occur at the time of the participant's routine clinical care visit. The duration of baseline and annual study assessments will range from 45 minutes (completion of core assessments only) to a maximum of 2.5 hours (completion of core assessments, extended assessments, optional assessments and/or participation in sub-studies). To ensure that the burden on the participant is not excessive, the maximum duration of assessments within a study visit will not exceed 2.5 hours.</p> <p>Assessments at baseline and annual follow-up visits include three components:</p> <ol style="list-style-type: none"> <li>1. Core Assessments: These data elements are mandatory for all participants at all sites.</li> <li>2. Extended Assessments: These data elements are to be collected to the extent possible from all participants at all sites.</li> <li>3. Optional Assessments (according to participant consent): Participating sites and individuals may choose to contribute these data elements.</li> </ol>

<p><b>Core Assessments</b></p>	<p>Written informed consent/parental permission/assent          Creation of the unique HD identification (HDID)          Review of Inclusion/Exclusion Criteria          Local diagnostic laboratory CAG report (if available)          Investigator and research genotyping determined classification of participants          Socio-demographic information          HD Clinical Characteristics (HDCC)          Medical history          Co-morbid conditions          Current therapies (Pharmacotherapy, Nutritional supplements, non-pharmacologic therapies)          Reportable Event monitoring</p> <p><b>Motor Assessments</b>          Unified Huntington’s Disease Rating Scale (UHDRS) 99          Motor          UHDRS Diagnostic Confidence Index</p> <p><b>Functional Assessments</b>          UHDRS ‘99 Total Functional Capacity          UHDRS ‘99 Functional Assessment Scale          UHDRS ‘99 Independence Scale</p> <p><b>Behavioral</b>          Problem Behaviors Assessment-Short (PBA-s)</p> <p><b>Cognitive Assessments</b>          Symbol Digit Modality Test          Stroop Color Naming          Stroop Word Reading          Categorical Verbal Fluency</p> <p><b>Research Genotyping</b> (conducted at the first visit for all new participants to the study or for participants from previous studies for whom a research genotype is not available)</p>
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<p><b>Extended Assessments</b></p>	<p><b>Global</b>        Global Clinical Impression</p> <p><b>Behavioral</b>        Hospital Anxiety/ Depression Rating Scale (HADS) &amp; Snaith Irritability Scale (SIS), combined        Columbia Suicide Severity Rating Scale (CSSRS)</p> <p><b>Cognitive</b>        Stroop Interference        Trail Making A &amp; B        Letter Verbal Fluency        Mini Mental State Examination (MMSE)</p> <p><b>Physiotherapy Outcome Measures</b>        Timed Up and Go (TUG)        30-second Chair Stand Test</p> <p><b>Quality of Life</b>        Short Form Health Survey-12 (SF-12)        Caregivers Quality of Life Questionnaire</p> <p><b>Health Economics</b>        Client Services Receipt Inventory (CSRI)        Work Productivity and Activity Impairment-Specific Health Problem Questionnaire (WPAI-SHP)</p>
<p><b>Optional Assessments</b></p>	<p>Family History        Biospecimens for biobanking</p>

<p><b>Sub-Studies</b></p>	<p>Apart from the study procedures associated with the main protocol of the Enroll-HD study, sub-studies involving a subpopulation of the Enroll-HD participants may be conducted under the Enroll-HD study umbrella. The purpose of these sub-studies is to provide a mechanism for establishing and validating novel assessment tools or assessment procedures by gathering data in specific HD populations and/or control populations and involves an iterative process of testing novel assessments, refining them and re-testing revised assessments. Participation in sub-studies is optional: participants must first consent to be approached to participate in sub-studies generally and then volunteer to participate in specific studies on a case-by-case basis. Sub-studies will only be implemented if the participant consents to this optional component <u>and</u> the burden of the study visit assessments does not exceed 2.5 hours. By definition, assessments for sub-studies are non-invasive and imply limited burden on the participant.</p> <p>Each sub-study will have a separate protocol that details study procedures, standard operating procedures for data collection and study coordination, and a data analysis plan. Ethical review for sub-study protocols listed below will be performed concurrently with the main Enroll-HD study protocol; future sub-study protocols will be submitted as minor protocol amendments. Informed consent for participation in sub-studies will be obtained within the informed consent forms for the main Enroll-HD study.</p> <p>Proposed sub-studies include:</p> <ol style="list-style-type: none"> <li>a. Pre-motor manifest HD - to further develop and validate outcome measures to detect and track alterations in prodromal stages of HD</li> <li>b. Advanced stage HD-to validate the “Advanced-stage UHDRS” for use in clinical and research practices</li> <li>c. Juvenile-onset HD-to develop and validate new scales and/or modify existing scales for outcomes of interest in this patient population</li> <li>d. Frontal behaviors-to validate existing measures of frontal behaviors (e.g. Apathy scales, FrSBe) in HD populations and develop sub-scales as outcome measures for trials</li> <li>e. Linguistic abilities- to characterize language impairment and assess syntactic abilities using the Sentence-Picture Matching Task</li> <li>f. General cognitive impairment- to validate the Montreal Cognitive Assessment for use in HD</li> <li>g. Tapping as outcome measure</li> <li>h. HD Quality of Life outcome measure-to develop and validate a patient-centered prototype health-related quality of life questionnaire specific for HD</li> <li>i. Physiotherapy outcome measures- to develop physiotherapy related outcome measures for use in future interventional studies</li> <li>j. Lifestyle factors- to examine the link between lifestyle factors</li> </ol>
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<b>Ancillary Studies</b>	Ancillary studies are defined as studies that are added on to the Enroll-HD studies. These studies may involve more invasive procedures and will entail separate protocols, ethical review, and informed consent forms. Ancillary studies can be added throughout the life of the Enroll-HD study.
<b>Ethical Considerations</b>	Independent ethics committees/institutional review boards will review and approve the protocol before any participant is enrolled. Informed consent is an unconditional prerequisite for patient participation in the study and procedures for obtaining informed consent will be based on participants' competency and will adhere to local regulations and requirements. Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing participant data. By signing the protocol, the institution and/or physician commit to complying with all related applicable international and local laws and regulations as well as any applicable Safe Harbor privacy principles.

## **2 BACKGROUND AND RATIONALE**

Huntington Disease (HD) is an autosomal dominant neurodegenerative disorder [1] that occurs worldwide. Prevalence estimates of HD vary by region and reported estimates range from 30,000 affected individuals in the United States [2, 3], 40,000 in Europe [4], 700 per 100,000 in the Lake Maracaibo region of Venezuela [5] and 6.29 per 100,000 in New South Wales, Australia [6]; an estimated 60,000 individuals in the United States, 80,000 individuals in Europe, and 25.2 per 100,000 population in New South Wales, Australia carry the HD mutation but are clinically unaffected as yet. HD is caused by an unstable expansion of a cytosine-adenine-guanine (CAG) trinucleotide repeat in exon-1 of the Huntingtin gene on chromosome 4 [7]. Individuals who inherit the mutant gene develop selective neuronal degeneration and eventually motor, cognitive and behavioral abnormalities that cause progressive loss of functional capacity and shortened life [1, 8-10]. HD is an invariably progressive neurodegenerative disorder characterized clinically by a movement disorder (typically chorea), behavioral disturbances, and cognitive impairment. The mean age of onset of characteristic abnormal movements in HD is approximately 39 years [9, 11-13] after which illness progresses steadily over a period of 15-25 years [8, 14]. The course of HD is relentless; to date, no treatment exists to alter the progression of the disease.

Since the gene mutation responsible for HD was identified in 1993 [7] progress has been made in understanding the pathogenesis of this disorder and in identifying targets for potential therapies modifying the natural course of the disease [15, 16]. Systematic screening efforts to identify compounds with disease modifying properties are under way [16-18] and there are reports of beneficial effects in model systems of HD [19, 20]. However, these results are yet to be translated to patients with HD. An integrated approach that incorporates basic, translational, and clinical research will help identify disease initiation and progression factors, explore promising experimental treatments, and develop state biomarkers. Collectively, this information will facilitate the planning and conduct of future clinical studies.

Enroll-HD integrates and builds upon two existing HD registries: the Cooperative Huntington Observational Research Trial (COHORT) based in North America and Australia [21], and REGISTRY – an observational study of the European Huntington-Disease Network (EHDN). Enroll-HD incorporates COHORT and REGISTRY sites and processes, and extends research activities to Latin America and Asia. Enroll-HD is a global enterprise that builds upon existing strong collaborative relationships among basic scientists, clinical investigators, and advocacy organizations. The primary objective of

Enroll-HD is to develop a comprehensive repository of prospective and systematically collected clinical research data (demography, clinical features, family history, genetic characteristics) and biological specimens (blood) from individuals with manifest HD, unaffected individuals known to carry the HD mutation or at risk of carrying the HD mutation, and control research participants (e.g., spouses, siblings or offspring of HD mutation carriers known not to carry the HD mutation). Enroll-HD is conceived as a broad-based and long-term project to maximize the efficiencies of non-clinical research and participation in clinical research while ensuring privacy and protections for consenting research participants. Enroll-HD's mandate includes provision of data to qualified scientists. Enroll-HD is funded by the CHDI Foundation, Inc., a not-for-profit organization that supports a variety of research projects seeking to find treatments for HD.

HD is a monogenetic disorder with the generational transmission of the disease from parent to offspring, regardless of gender {Huntington, 1872 #16}. The length of the unstable, expanded CAG repeat within the coding region of the HD gene at 4p 16.3 explains many of the genetic features of the disorder, including the variable age at onset, the tendency for juvenile disease to be inherited from fathers, and the (rare) appearance of new mutations [11, 12, 22, 23]. However, the size of the CAG repeat accounts for only about 60-70% of the variance in age at onset and recent studies suggest that other modifier genes may influence age at onset [24]. While the search for modifying genes has been limited thus far to age at onset of motor signs as the phenotype (see e.g. [25, 26]), it is clear that HD displays variability in other features of disease expression, including psychiatric manifestations (e.g., depression, psychosis) and cognitive impairment (e.g., impairment of executive function and/or immediate memory).

Studies of genetic modifiers for outcomes such as disease progression and neuroimaging abnormalities have been hampered by limited availability of high quality prospectively collected longitudinal data. Enroll-HD will provide a information over a wide range of HD phenotypes (e.g., early and late onset, chorea predominant and akinetic/dystonic presentations), including clinical assessments and levels of RNA, protein and metabolites, for studying modifier genes with the goal of identifying and validating therapeutic targets. Further, DNA samples will facilitate genome-wide search for polymorphisms outside the HD gene. Family history data collected as part of Enroll-HD will facilitate assessment of phenotypic variation within families, degree of heritability, and enable sib pair analysis. Thus, the relationships of individual polymorphisms/genes with disease manifestation, progression, and response to treatment can be explored using

genetic association strategies that leverage the combination of enriched phenotypic and genotypic information that will be collected in Enroll-HD.

The goal of Enroll-HD is to build a large and rich database of clinical information and biospecimens that will serve as a basis for future studies aimed at developing tools and biomarkers for progression and prognosis, identifying clinically relevant phenotypic characteristics, and establishing clearly defined endpoints for interventional studies.

### **3 STUDY OBJECTIVES**

Objective 1: To improve the understanding of the dynamic phenotypic spectrum and the disease mechanisms of HD by:

- a. collecting natural history data covering the cognitive, behavioral and motor domains permitting estimates of rates of progression in HD and allowing insights into the neurobiology of HD,
- b. collecting data and biologic samples to identify genetic and environmental factors influencing and/or modifying the HD phenotype and disease progression, and
- c. promoting interrogatory studies that may provide clues to the pathogenesis of HD.

Objective 2: To promote development of evidence-based guidelines to inform clinical decision making and improve health outcomes for the participant/family unit by:

- a. assisting in the identification of beneficial interventions (clinical, pharmacotherapeutic, non-pharmacologic),
- b. facilitating the dissemination and implementation of currently proposed best clinical practices,
- c. providing a platform for conducting outcome research, and
- d. promoting exploratory data analysis projects that may identify processes to further improve health care of affected individuals and their families

Objective 3: To provide a platform to support the design and conduct of clinical trials by

- a. providing a resource to identify, develop and qualify novel assessment tools, clinical endpoints and biomarkers,
- b. collecting longitudinal data to inform disease modeling studies,
- c. facilitating the identification of potential trial participants, and
- d. informing the selection of potential trial participants using data to estimate and quantify slopes/rates of disease progression (providing “run-in” data).

### **4 STUDY DESCRIPTION**

Enroll-HD is a prospective observational multicentre multi-national cohort study to be conducted in multiple native languages. Study procedures include annual assessments conducted during study visits that may coincide with regularly scheduled clinic visits.

The study does not include interventional procedures outside of normal clinical care, nor does it include experimental therapies.

#### **4.1 Study Period**

Enroll-HD is an open-ended, prospective study. Participants will be asked to participate in as many annual study visits as possible.

#### **4.2 Study Population**

This study aims to recruit all participants who are eligible and willing to participate with a goal of enrolling approximately one-third of the HD affected population in each study region (North America, Latin America, Europe, Asia, Australia and New Zealand). Both males and females will be included in this study. Individuals 18 years of age and older will be asked to participate in all aspects of the study. For individuals under the age of 18 years, only those with clinically diagnosed features of HD in the setting of a confirmatory genetic test result may be included in this study. There are no restrictions on ethnicity or race. Past experience in HD research has suggested a lower prevalence of HD in non-Caucasian populations, although there are no definite racial predispositions and the disease is found throughout the world.

##### **4.2.1 Inclusion Criteria**

Informed consent from the potential participant or legal representative is a pre-requisite for study participation. Individuals eligible to participate in Enroll-HD will be classified into two major categories:

1. Carriers: This group comprises the primary study population and consists of individuals who carry the HD gene expansion mutation.
2. Controls: This group comprises the comparator study population and consists of individuals who do not carry the HD gene expansion mutation.

These two major categories can be further subdivided into six different subgroups of eligible individuals:

- a. **Manifest/Motor-manifest HD**: Carriers with clinical features that are regarded in the opinion of the investigator as diagnostic of HD.
- b. **Pre-Manifest/-Motor-manifest HD**: Carriers without clinical features regarded as diagnostic of HD.
- c. **Genotype Unknown**: This group includes a first or second degree relative, i.e., related by blood to a carrier, who has not undergone predictive testing for HD and therefore has an undetermined carrier status.

- d. Genotype Negative: This group includes a first or second degree relative, i.e., related by blood to a carrier, who has undergone predictive testing for HD and is known not to carry the HD expansion mutation.
- e. Family Control: Family members or individuals not related by blood to carriers (e.g., spouses, partners, caregivers).
- f. Community Controls: Individuals unrelated to HD carriers who did not grow up in a family affected by HD. Data collected from community controls will be used for generation of normative data for sub-studies.

For the purposes of the Enroll-HD study the terminology 'manifest/motor-manifest' vs 'pre-(motor)-manifest' will be used to describe the population of HD expansion mutation carriers. It is acknowledged that recent data from PREDICT-HD and TRACK-HD provide strong evidence for the concept of a prodromal stage of HD with measurable abnormalities in several domains including magnetic resonance imaging and quantitative motor tests years before a conventional HD diagnosis based on the emergence of diagnostic motor signs. However, the same studies support the concept of a stage in the life of HD expansion mutation carriers during which no features distinguishing mutation carriers from non-mutation carriers can be identified. In addition, it is acknowledged that dividing a continuum of disease manifestations into qualitatively distinct stages (pre-motor-manifest vs. motor-manifest) is somewhat arbitrary and that the criteria defining such stages are a matter of ongoing debates. However, given the need to communicate that carriers of the HD expansion mutation irrespective of the presence or absence of clinical features as well as people at risk are invited to participate in Enroll-HD, given the wide use of the pre-manifest/manifest terminology, and given the increased use of stage-dependent assessment tools in the current version of the protocol this terminology is employed purely for practical reasons.

Participant status will be captured in the study database using 2 variables: 1) Investigator Determined Status: this will be based on clinical signs and symptoms and genotyping performed as part of medical care and will be updated at every visit and 2) Research Genotyping Status: this will be based on genotyping conducted as part of Enroll-HD study procedures. Based on research genotyping, participants will be reclassified under this variable from Genotype Unknown to 'Carriers' or 'Controls'. Investigators and participants will be blinded to this reclassification.

#### **4.2.2 Exclusion Criteria**

1. Individuals who do not meet inclusion criteria
2. Individuals with choreic movement disorders in the context of a negative test for the HD expansion mutation

3. For Community Controls: those individuals with a history of or concurrent major central nervous system disorder will be excluded (e.g. stroke, Parkinson disease, Multiple Sclerosis, etc.)

### **4.3 Study Enrollment**

#### **4.3.1 Participant Identification, Recruitment**

Patients with HD and their family members will be recruited from specialty clinics (Human Genetics, Neurology, Psychiatry) that advise and treat people affected by HD. In addition, in some areas community clinics and neurologists who see HD patients will recruit participants for this study. The research staff at each site will identify potentially eligible participants and inquire as to their willingness to participate in this study. Participants will also be requested to forward an invitation to their relatives to consider taking part in Enroll-HD. Participants may also receive information about the study through a website, clinical practices, support groups, advocacy newsletters, etc. and place a direct request to be considered for participation in the study. In addition, efforts will be made to provide educational information on the Enroll-HD study web portal.

Community controls will be identified, using Institutional Review Board (IRB)/Independent Ethic Committee (IEC)-approved advertisements, flyers and newsletters, by study site staff with the support of the Enroll-HD operational staff. For normative data collections in the context of sub-studies, appropriately qualified members of the sub-study team (i.e., neuropsychologists, study site coordinators aside from the PI, supported by Enroll-HD operational staff) are responsible for the recruitment of community controls. IRB/EC-approved compensation that reimburses travel expenses may be provided.

#### **4.3.2 Consent Process**

Information about Enroll-HD will be provided in oral and written form to the participants complementing information available to them from the resources mentioned above. Informed consent is an unconditional prerequisite for participation in the study and procedures for obtaining informed consent will be based on participants' competency and age and will adhere to local regulations and requirements and Good Clinical Practice.

An informed consent form (ICF) will be signed by all competent participants defined as individuals with the cognitive and mental capacities, as determined by the site investigator, to understand the nature and purpose, procedures, risks and benefits of the study and have a non-coerced desire to participate.

For individuals with impaired cognitive and mental function, consent will be obtained from a legally acceptable representative. A representative may include the spouse, a person specifically appointed to take care of the legal interests of the participant, an individual with guardianship, and a health care proxy, provided consenting for research studies is within the legal scope of the proxy's delegated responsibilities. The representative must have the cognitive and mental capacities (as determined by the site investigator) enabling him/her to understand the procedures, risks, and benefits involved with the study.

Given the nature of the disease, participants with HD may lose mental capacity during the course of the study; therefore, a recommendation will be made to all participants with HD to discuss their future study participation wishes with the representative. In the case of obvious retraction of assent to participate in the study, consent will be formally reassessed with the representative.

The consent may be given and the form signed, at a single visit or at a future visit to the study site, based on the choice of the participant, and, where mandated, on the choice of the representative.

Underage participants will be defined by local regulations in each of the selected countries. Underage participants that reach the local legal age for providing informed consent during follow-up will be re-consented as soon as feasible, i.e., at the next follow-up time-point. If at the age of majority the participant is not able to provide consent due to mental incapacity the procedures for obtaining consent in incapacitated adults will be followed.

Consent will be obtained from parent/legal guardian for all underage participants and assent will be obtained as described below; however, where applicable, these procedures will be modified to comply with local regulations and requirements.

- <7 years: written parental permission will be obtained and documented.
- 7 to 12 years: written parental permission and verbal assent by the participating child will be obtained and documented.
- 13 to 17 years: parental permission with written assent by the participating child will be obtained and documented through signature.

Signed consent/assent forms will be stored in a designated secure location at the site. A signed copy of the consent/assent will be provided to the participant/parent/guardian and, if applicable, their authorized representative. The informed consent process will be

documented in the medical record for patients and in a research chart for other participants (as appropriate).

#### **4.3.3 Participant Withdrawal**

Participants are free to withdraw from the study at any time. Reason for study discontinuation or withdrawal will be collected; however, reasons for withdrawal of consent do not have to be disclosed. Unless otherwise requested by the participant, all data and biosamples obtained up to that point will be retained. Only on explicit request by a participant will all biosamples still stored at the central biorepository at the time of the withdrawal be discarded. Data collected to this point will be de-identified (i.e., made untraceable) and maintained in the database. In addition, an investigator may withdraw participants from the study at any time if he or she feels that it is in the best interest of the participant.

## 5 DATA COLLECTION AND ASSESSMENTS

Study visits will take place annually and may occur at the time of the participant's routine clinical care visit. The duration of baseline and annual study visits will range from 45 minutes (completion of core assessments only) to a maximum of 2.5 hours (completion of core assessments, extended assessments, optional assessments and/or participation in sub-studies). To ensure that the burden on the participant does not change, the maximum visit will be 2.5 hours.

Assessments at baseline and annual follow-up visits include three components (see Table 1):

1. Core Assessments: These data elements are mandatory for all participants at all sites.
2. Extended Assessments: These data elements are to be collected to the extent possible from all participants at all sites.
3. Optional Assessments (according to participant consent): Participating sites and participants may choose to contribute these data elements.

### 5.1 Training

All assessments will be performed by trained clinical personnel. Training and certification will be conducted using a variety of training methods including practice videos, test assessments to train and certify raters, training sessions during investigator meetings, on-line using training videos, and didactic teaching methods. In addition, participating sites will be provided with manuals detailing instructions for implementing, administering and scoring study instruments. Study personnel will undergo periodic recertification. To the extent possible, each site will be asked to use the same individual rater to administer study instruments to a particular participant for the duration of the study so as to maximize internal consistency.

**Table 1: Enroll-HD Assessments**

Assessments	Core	Extended	Optional
Written informed consent/ parental permission/assent* (Section 4.3.2)	X		
Creation of the unique HDID* (Section 7.5)	X		
Review of Inclusion/Exclusion Criteria* (Section 4.2)	X		
Local diagnostic laboratory CAG report (if available)*	X		
Investigator and research genotyping determined classification of participant§ (Section 4.3.1)	X		

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Socio-demographic information <sup>§</sup>	X		
HD Clinical Characteristics (HDCC) <sup>§</sup>	X		
Medical history <sup>§</sup>	X		
Co-morbid conditions <sup>§</sup>	X		
Current therapies <sup>§</sup> Pharmacotherapy Nutritional supplements Non-pharmacologic therapies	X		
Reportable event monitoring <sup>§</sup> (Section 5.5)	X		
<b>Motor</b> (Section 5.2.1)			
UHDRS '99 Motor	X		
UHDRS '99 Diagnostic Confidence Index	X		
<b>Functional</b> (Section 5.2.2)			
UHDRS '99 Total Functional Capacity	X		
UHDRS '99 Function Assessment Scale	X		
UHDRS '99 Independence Scale	X		
<b>Behavioral</b> (Sections 5.2.3 & 5.3.1)			
Problem Behaviors Assessment-Short (PBA-s)	X		
Hospital Anxiety/ Depression Rating Scale (HADS)		X	
Snaith Irritability Scale (SIS)		X	
Columbia Suicide Severity Rating Scale (CSSR)		X	
<b>Cognitive</b> (Sections 5.2.4 & 5.3.2)			
Symbol Digit Modality Test	X		
Stroop Word Reading	X		
Categorical Verbal Fluency	X		
Stroop Color Naming	X		
Stroop Interference		X	
Trail Making A & B		X	
Letter Verbal Fluency		X	
Mini Mental State Examination (MMSE)		X	
<b>Global Assessment</b>			
Global Clinical Impression		X	
<b>Physiotherapy Outcome Measures</b> (Section 5.3.3)			
Timed Up and Go (TUG)		X	
30-second Chair Stand Test		X	
<b>Quality of Life</b> (Section 5.3.4)			
Short Form Health Survey-12 (SF-12)		X	

Companion Quality of Life Questionnaire		X	
<b>Health Economics</b> (Section 5.3.5)			
Client Services Receipt Inventory (CSRI)		X	
Work Productivity and Activity Impairment-Specific Health Problem Questionnaire (WPAI-SHP)		X	
<b>Research Genotyping</b> (conducted at the first visit for all new participants to the study or for participants from previous studies for whom a research genotype is not available) (Section 5.2.5)	X		
<b>Family History</b> † (Section 5.4.1)			X
<b>Biospecimens for biobanking</b> † (Section 5.4.2)			X

\* Assessments performed only at the baseline visit

§ Assessments performed at the baseline visit and re-evaluated and updated at subsequent annual visits

† Optional participation requiring explicit informed consent

## 5.2 Core Assessments

The Core Assessments are data elements that are required for all participants at all sites to be collected at baseline and annual follow-up visits. The planned assessments and instruments are described in detail in subsequent sections. In addition, information will be collected regarding co-morbid conditions, concurrent medications, and HD clinical characteristics and treatment including pharmaco-therapeutic, non-pharmacologic, nutritional supplements, physiotherapy, etc.

For participants under the age of 18 who have clinically diagnosed features of HD, site investigators are encouraged to consider the use of specific Juvenile Huntington’s Disease (JHD) assessment tools evaluated as part of the JHD sub-study (Section 9.1.3); if a participant did not consent to take part in the sub-studies, it will be left to the discretion of the site investigator to determine if the child is able to complete the standard cognitive assessment, functional assessment, independence scale, and functional capacity assessments.

Several subscales of the Unified Huntington’s Disease Ratings Scale 99 (UHDRS ‘99) will be used to perform core assessments. The UHDRS has undergone extensive testing of reliability and internal consistency and is used widely in HD studies [27-32] Modified versions of the UHDRS scale and additional scales (developed de-novo or re-designed for HD) may be used as appropriate for describing the HD phenotype and measuring progression in HD expansion mutation carriers (e.g., juvenile-onset HD, pre-motor-manifest stages of HD), or different degrees of capacity (e.g., advanced stages of HD).

### **5.2.1 Core Motor Assessments**

The Motor and Diagnostic Confidence Index subscales of the UHDRS will be used to characterize the clinical HD motor phenotype and to capture the diagnostic confidence of the rater. The motor section of the UHDRS assesses motor features of HD with standardized ratings of oculomotor function, dysarthria, chorea, dystonia, gait, and postural stability.

### **5.2.2 Core Functional Assessments**

The Total Functional Capacity, Functional Assessment and Independence Subscales of the UHDRS '99 will be used to assess participants' functional status. The Total Functional Capacity scale has established psychometric properties including inter-rater reliability and validity, based on radiographic measures of disease progression.

### **5.2.3 Core Behavioral Assessments**

The Problem Behavioral Assessment Short Version (PBA-s) will be used to perform behavioral assessments. This instrument measures frequency and severity of symptoms related to altered affect, thought content and coping styles [33, 34]. This semi-structured interview includes items that cover an extensive range of behaviors including: depressed mood, low self esteem, anxiety, suicidal thought, aggressive behavior, irritability, perseveration, compulsive behaviors, delusions, hallucinations, and apathy. The interviewer rates frequency and severity of the behavior over the past month. Frequency and severity are assessed as independent qualifiers of positively affirmed behavioral symptoms. The PBA-s is meant to be administered in the presence of a companion; however, there is an option to perform this assessment in the absence of a companion and to record this as part of the instrument.

It is anticipated that all participating sites will have existing collaborative relationships with psychiatry practices, such that in the event that suicidal ideation is detected while administering the PBA-s to a participant, prompt referral for psychiatric evaluation and/or management is available.

### **5.2.4 Core Cognitive Assessments**

Cognition will be assessed using the Categorical Verbal Fluency Test, Symbol Digit Modality Test and Stroop Color and Word Reading Test [27, 35]. Verbal fluency is a commonly used neuropsychological test which examines the ability to spontaneously produce words orally within a fixed time span. For category fluency, words must be produced according to semantic constraints. The measure of performance used will be the number of correctly generated words within 60 seconds. The Symbol Digit Modality Test

(SDMT) involves a simple substitution task. Using a reference key, the examinee has 90 seconds to pair specific numbers with given geometric figures. The score is the number of correct responses achieved in 90 seconds. The Stroop Color and Word Reading tests are commonly used neuropsychological tests. They involve naming colors (e.g., red, green, blue) and reading the words for colors in black ink.

### **5.2.5 Research Genotyping**

Ten ml of peripheral blood will be collected in a yellow topped acid citrate dextrose solution (ACD) tube and shipped by a fast courier service to the central biorepository facility. The sample will be assigned a unique identifier and DNA will be extracted using standard procedures. The central biorepository facility will process blood for DNA extraction. Routine quality control studies will be conducted to estimate the quality and integrity of the DNA. Genotyping of the DNA will be performed according to standard procedures including CAG repeat sizing using two sets of primer pairs [36, 37]. The DNA genotyping will be performed in a research lab and therefore, the results are experimental data.

An independent Data Safety Monitoring Committee (DSMC) will monitor the CAG testing procedures to ensure high quality and also monitor testing results compared to available data on local results for individual participants. Individual results will not be reported to the sites or to the participants unless the DSMC (following review of data from local genetic testing and central research genotyping) decides to alert the study site of important discrepancies between local and central laboratory results that are potentially clinically relevant. In these rare cases where a potentially clinically relevant difference exists, the DSMC will notify the investigator directly, who will make the final decision on how to address the discrepancy, based on their best clinical judgment. If a participant decides to seek predictive genetic testing for the length of the CAG repeat while participating in this study, he/she may do so through the available HD predictive testing centers. In regions where the costs of genetic testing are not covered by the respective regional health care plan or national health service, resources may be made available to ensure that the internationally recommended procedures for predictive and diagnostic genotype testing can be followed and that the molecular test can be performed.

### **5.3 Extended Assessments**

These data elements are to be collected to the extent possible on all participants at all sites.

### **5.3.1 Extended Behavioral Assessments**

#### *5.3.1.1 Hospital Anxiety and Depression Scale (HADS)*

The Hospital Anxiety and Depression Scale (HADS) is a self-report rating scale [38-40]. The HADS offers a brief rating of depression and anxiety symptoms that reflects primarily mood rather than cognitive and somatic symptoms. The HADS scale has 14 items, seven measuring anxiety and seven measuring depression producing separate anxiety and depression sub-scores. Each item is rated on a four-point scale.

#### *5.3.1.2 Snaith Irritability Scale (SIS)*

The SIS is a brief rating scale of irritability by self-report.[41]. The scale is composed of eight items each rated on a four-point scale. Four items are focused on inward irritability and four items are focused on outward irritability.

#### *5.3.1.3 Columbia Suicide Severity Rating Scale (CSSRS)*

The Columbia Suicide Severity Rating Scale (CSSRS) was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and monitor suicidal events during a treatment period [42, 43]. It can be administered by a rater following a structured interview. The interview can provide an overall assessment of suicidal ideation as well as suicidal behavior in order to generate a summary measure of suicidality. All personnel involved in this assessment will be informed of the risk indicators and local protocols for appropriate referrals.

### **5.3.2 Extended Cognitive Assessments**

#### *5.3.2.1 The Stroop Interference Test*

The Stroop Interference Test is a neuropsychological test of cognitive flexibility and resistance to interference. It involves reading words of colors (e.g. red, green blue) where the word color is written in a different color ink.

#### *5.3.2.2 The Trail Making Tests*

The Trail Making Tests are neuropsychological tests measuring visual attention and task switching.

#### *5.3.2.3 The Mini Mental State Examination (MMSE)*

The Mini Mental State Examination (MMSE) is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language [44].

### **5.3.3 Physiotherapy Outcome Measures**

#### *5.3.3.1 Timed Up and Go (TUG)*

The timed up and go test is a measurement of mobility. It includes a number of tasks such as standing from a seating position, walking, turning, stopping, and sitting down which are all important tasks needed for a person to be independently mobile. The participant is asked to stand up from a standard chair and walk a distance of approximately 10 feet (measure as 3 meters), turn around and walk back to the chair and sit down again. The individual uses his/her usual footwear and can use any assistive walking device they normally use, such as a cane. The person is seated with his/her back to the chair, their arms resting on the arm rests, and any walking aid they may use should be in hand. Timing, using either a wristwatch with a second hand or a stop watch, begins when the individual starts to rise from the chair and ends when he/she is once again seated in the chair. The normal time required to finish the test is between 7 – 10 seconds. The TUG has been studied in HD and has been shown to predict falls in this population.

#### *5.3.3.2 30 Second Chair Stand Test*

The 30 second chair stand test provides a measurement of a person's lower body (particularly legs) strength. This is associated with the ability to perform lifestyle tasks such as climbing stairs, getting in and out of a vehicle or bath. The following instructions are provided to the participant:

1. Sit in the middle of the chair.
2. Place your hands on the opposite shoulder crossed at the wrists.
3. Keep your feet flat on the floor.
4. Keep your back straight.
5. On the signal to begin rise to a full stand position and then sit back down again.
6. Repeat this for 30 seconds.

Count the number of times the client comes to full standing position in 30 seconds. If the participant is over halfway to a standing position when 30 seconds have elapsed count it as a stand.

### **5.3.4 Quality of Life Assessments**

#### *5.3.4.1 Short Form Health Survey-12*

The Short Form Health Survey-12 (SF-12) contains 12 items that measure each of the eight concepts included in the SF-36 [45]. The SF-12 is extensively used in large

population health surveys as a brief, reliable measure of overall health status. The 1-week recall version will be used.

#### *5.3.4.2 Caregivers Quality of Life Questionnaire*

The Caregivers Quality of Life Questionnaire was developed as part of the REGISTRY study. This administered instrument that measures caregiver reactions, including perception and emotional feeling with regards to care giving. This general caregiver instrument provides direct evidence of impact on caregiver quality of life.

### **5.3.5 Health Economic Assessments**

#### *5.3.5.1 Client Services Receipt Inventory (CSRI)*

The Client Services Receipt Inventory (CSRI) questionnaire provides information on service utilization by collecting retrospective information on service related issues. It is an established tool and has been used in a range of research studies including mental health outreach services, community nursing services and community care of older people and people with challenging behavior [46]. The questionnaire schedule is designed for interviewer/researcher administration with the person receiving the services assisted by their main caregiver as required.

#### *5.3.5.2 Work Productivity and Activity Impairment-Specific Health Problem Questionnaire*

The Work Productivity and Activity Impairment-Specific Health Problem Questionnaire (WPAI-SHP) is a six-item questionnaire that measures effect of specific health problems on number of hours worked and the number of hours missed from work [47]. It also measures the effect of disease on productivity and regular activities. Decreases in values on each part indicate improvement. The sum of work time missed and impairment at work yields the overall work impairment (productivity loss) score; scores are expressed as percentage of impairment and/or productivity loss, with higher scores indicating greater impairment.

## **5.4 Optional Assessments**

Participating sites and individuals may choose to contribute these data elements. It requires that the participant provide specific consent to participate in these assessments.

### **5.4.1 Family History Questionnaire (FHQ)**

Participants who consent to this optional component will be asked to volunteer data covering 4 generations [i.e. information on their siblings and (if applicable) on their

spouse(s), data on their parents and the parental siblings (i.e., aunts and uncles) on the affected side of the family, data on their grandparents (i.e., the parents of their HD affected parent), and (if applicable) data on their children as well as on the offspring of their siblings (i.e., nieces and nephews)]. The purpose of the FHQ is (1) to render linked biosamples or data sets identifiable while protecting the privacy of all donors, (2) to obtain a family tree as an important part of standard medical care and (3) to provide a basis for studying the heritability of phenotypical traits in HD families as well as the intergenerational stability of the expansion mutation.

Participants and investigators will be asked to provide the following information on each person within the family tree:

- Gender
- Year of birth
- Vital status: if deceased, year and cause of death
- HD status (manifest/pre-manifest carrier/not a carrier & degree of certainty of the status designation)
- Availability of local DNA samples

No identifying information will be collected. From these data a family tree will be generated using appropriate software. Within this family tree, the symbols representing those members of the family who consented to participate in Enroll-HD will be annotated with their participant IDs; family members who did not consent to participate in Enroll-HD will be represented with symbols without an annotated participant ID.

#### **5.4.2 Biospecimens**

For participants who consent to donation of biosamples, up to 40 ml of blood will be collected at each annual visit for storage in a central biospecimen repository (BioRep). Specimens will be de-identified for storage and the central repository will have no access to identifying data. Participants may opt to participate at only the baseline visit or at any of the subsequent annual follow up visits. The banked blood will be used to generate lymphoblastoid cell lines, to extract DNA and cryopreserve lymphocytes.

A 10 ml yellow top ACD tube will be used for lymphoblastoid cell line creation and appropriate testing for viability and contamination. A second 10 ml yellow top ACD tube will be used for lymphocyte isolation and cryopreservation.

At specific sites with required specimen processing capabilities and proper training, plasma separation will be performed. In brief, blood will be drawn in a 9.5 ml EDTA tubes and centrifuged in a refrigerated within 30 minutes of blood draw. Plasma is

aliquotted into sterile cryotubes and placed in a -80°C freezer and subsequently shipped on dry ice using an overnight courier service. Shipping labels and detailed packaging instruction will be provided by the central biospecimen repository.

#### **5.4.3 Future Contact Regarding Research Studies**

Participants 18 years of age or older will be given the option of allowing the site research staff to maintain their name and contact information so that the site research staff may contact them regarding future participation in HD studies. This information will be kept confidential and will be stored at the site, separate from the Enroll-HD study database.

#### **5.4.4 Discussion of Post-Mortem Donation of Biological Materials**

As part of the informed consent process, participants will be alerted to the option of donating post-mortem tissues as part of Enroll-HD; as a first step, participants will be asked for permission to be approached to discuss the local options for post mortem donation of biological materials for research; the procedures for the collection and banking of post-mortem tissues will vary in compliance with the applicable regional regulations and will be presented in a separate, regional document.

#### **5.4.5 Transfer of Data from Other HD Studies and Trials**

HD is a slowly progressive, lifelong disease. Assessments of HD patients have been systematically collected using standard tools (e.g., UHDRS) in the course of their normal clinical visits or during previous or ongoing HD-related clinical studies or trials. In order to allow the HD research community to have access to these systematically collected clinical data recorded prior to Enroll-HD participants will be asked to provide permission for incorporation of a copy of clinical and laboratory data collected from them prior to the date of enrollment in Enroll-HD for integration within the Enroll-HD study database.

The collection of retrospective data will significantly enrich the clinical data available on this HD cohort. The combination of retrospective and prospective clinical data will provide a unique resource compiling all clinical data on a given participant in chronological order. These data can be used to understand more about an individual's trajectory for each parameter over the natural course of HD ('run-in data') and will help to quantify trial participation effects at the level of individual participants and individual raters. Consent to providing these data implies no additional burden on the participant.

#### **5.4.6 Transfer of Biospecimens from Other HD Studies and Trials**

For similar reasons participants will be asked to provide permission for transfer of biospecimens collected as part of other HD (previous or ongoing) studies and trials to the Enroll-HD biospecimen repository.

#### **5.4.7 Participation in Sub-Studies**

Apart from the study procedures associated with the main protocol of the Enroll-HD study, sub-studies involving a subpopulation of the Enroll-HD participants may be conducted under the Enroll-HD study umbrella. The purpose of these sub-studies is to provide a mechanism for establishing and validating novel assessment tools or assessment procedures by gathering data in specific HD populations and/or control populations and involves an iterative process of testing novel assessments, refining them and re-testing revised assessments.

Participation in sub-studies is optional: participants must first consent to be approached to participate in sub-studies generally and then volunteer for (i.e., consent) to participate in specific studies on a case-by-case basis. Sub-studies will only be implemented if the participant consents to this optional component and if the burden of the study visit assessments does not exceed 2.5 hours. By definition, assessments for sub-studies are noninvasive and imply limited burden on the participant.

These sub-studies are intended to better inform about specific and/or rare clinical phenotypes not presently captured in the established standardized assessments. Validation of assessment tools implies exploring the clinical metrics of the tool as well as inter-rater reliability. A systematic analysis of each item of the assessment tools used will allow the development of improved, more mature assessment tools. In a first pass, cross-sectional data will be gathered, and in a second pass, data gathering will extend to longitudinal data to look at the rate of changes in the various assessments.

A brief description of the currently proposed sub-studies is listed below and outlines are provided in the appendices. Each sub-study will have a separate protocol that details study procedures, standard operating procedures for study coordination, and a data analysis plan. Ethical review for sub-study protocols will be performed concurrently with the main Enroll-HD study protocol. Informed consent for the sub-studies will be obtained within the informed consent forms for the main Enroll-HD study.

New sub-studies may be proposed by qualified researchers and will need to be reviewed and approved by the Enroll-HD Steering Committee and will be implemented only after obtaining appropriate IRB/EC approvals.

Enroll-HD Sub-studies (see Appendix 1 for detailed descriptions):

- a. Pre-motor manifest HD - The objective of this sub study is to further validate clinical outcome measures to detect and track alterations in prodromal stages of HD. It will include participants with pre-motor manifest HD and will test a battery

- of assessments, developed in other HD studies including PREDICT-HD [48], TRACK-HD [49], and FurST-pHD and, to establish and evaluate a battery of quantitative motor, cognitive, oculo-motor, functional and behavioral domains..
- b. Advanced stage HD - The objective of this sub-study is to validate the “Advanced-stage UHDRS” for use in clinical and research practices. It will include participants with a UHDRS ‘99 Total Functional Capacity Score of  $\leq 5$ . The 4 components of the Advanced-HD scale (motor function, somatic domain, cognitive assessment, behavioral assessment) will be compared with the standard UHDRS ‘99 scale to assess progression of disease at one year.
  - c. Juvenile-onset HD - The objective of this sub-study is to develop and validate new scales and/or modify existing scales for outcomes of interest in Juvenile-onset HD. It will include participants with motor onset HD aged  $\leq 20$  years. Rasch analysis will be used to assess performance and to refine the UHDRS-JD rating scales. Semi-structured interviews and diaries will be used to collect data to inform the development of additional scales.
  - d. Frontal behaviors (FrSBE, Irritability and Apathy) - The objective of this sub-study is to validate existing measures of frontal behaviors in a HD population and develop sub-scales as outcome measures for trials. This sub-study will include confirmed HD gene mutation carriers who are  $\geq 18$  years of age. Data will be collected to understand the nature and course of frontal-type behaviors in HD and to identify scales that can be used as clinical outcome measures in interventional trials.
  - e. Linguistic Abilities - The objective of this sub-study is to characterize language impairment and assess syntactic abilities. It will include participants in the early stages HD. Syntactic abilities will be assessed using the Sentence Picture Matching Task with longitudinal data collection over a 1-year period.
  - f. Validation of the Montreal Cognitive Assessment (MoCA) - The aim of this sub-study is to validate the Montreal Cognitive Assessment. It will include participants at all stages of HD. A semi-randomized design will be used to assess cross-sectional and longitudinal sensitivity of this measure and to examine its utility in detecting and tracking global cognitive change.
  - g. Tapping - The objective of this study is to validate a finger/hand-tapping task as a measure of cognitive change. It will include participants at all stages of HD. All currently used tapping tasks in HD will be systematically reviewed to facilitate choice of a task that measures motor speed, dexterity and psychomotor speed and is sensitive and reliable.
  - h. HD Quality of Life (HD QoL) - The aim of this sub-study is to develop and validate a patient-reported health-related quality of life questionnaire specific for HD. It will

include participants at all stages of HD. The psychometric properties of the HD QoL instrument will be tested.

- i. **Physiotherapy outcome measures** - The objective of this sub-study is to develop physiotherapy-related outcome measures for use in future interventional studies. It will include participants at all stages of HD. A range of physiotherapy-related assessments (6-Minute Walk Test, 10-Minute Walk Test, Timed “Up and Go”, Physical Performance Test, Rivermead Mobility Index, Barthel Index, Berg Balance Scale, Romberg and Sharpened Romberg Test, Performance Oriented Mobility Assessment, Four Square Step Test, International Physical Activity Questionnaire) will be examined for utility as potential outcome measures.
- j. **Lifestyle factors** - The objective of this sub-study is to examine prospectively the link between lifestyle factors, age at onset of Huntington’s disease and rate of progression.

#### **5.4.8 Ancillary Studies**

Ancillary studies are added on to the Enroll-HD study and utilize data elements collected in Enroll-HD. This sharing of data elements will allow for decreased burden on research participants who wish to participate in ancillary studies. These studies may involve more invasive procedures and will be described in separate protocols, undergo separate ethical review, and informed consent forms. Ancillary studies can be added throughout the life of the Enroll-HD study.

#### **5.5 Reportable Event Monitoring**

Reportable events include discrepancies between research and diagnostic genotyping, suicide attempts, completed suicide, mental health events requiring hospitalization, and death from any cause. When a reportable event occurs, site staff must fill out the Reportable Events electronic Case Report Form (eCRF) and notify the operations center, by telephone, within 48 hours of becoming aware of the event. Information to be provided for each reportable event includes: investigator’s name/study center, participant number, date of event, description of event, and intervention. Sites will have to fill out the eCRF upon receipt of an event report, the operations center will notify the Principal Investigator, Site Investigator/Coordinator (for the site who called in the Reportable Event), and DSMC. Site investigators may be required to notify local ethics committees of these events as well.

## **6 STATISTICAL METHODS**

### **6.1 Sample Size**

In performing an observational cohort study, the larger the sample size used for data analysis, the more applicable the results are to the population as a whole. Therefore, Enroll-HD will allow each site to enroll as many participants as are eligible and willing to participate. As described in the rationale, Enroll-HD is a cooperative effort to build a large linked dataset of clinical data and biosamples, with the aim of validating results of previous studies with smaller sample sizes and enabling testing of new hypotheses.

While each project proposal defining a specific outcome or endpoint will include a sample size calculation and/or power analysis specific to the objectives of that particular study, in general, the sample size and open ended enrollment is planned a) to facilitate genetic modifier studies that require large numbers to reliably identify genes of interest and their modifiers, b) to identify distinct phenotypes that are infrequent and therefore require large numbers for detection, c) to explore a diversity of environmental modifiers and gene-environment interactions, and d) to build disease models to study prognostic factors and rates of progression.

Since all questions will not necessarily require the entire sample of participants, only a subset of assessments are delineated as core assessments and required on all participants at all sites. Extended assessments are to be collected on most participants as often as possible, but due to the planned large number of participants, it is anticipated that even with missing data, there will be sufficient number of participants with extended assessments, and therefore, sufficient power for proposed analyses.

### **6.2 Data Analysis**

Descriptive analyses will be conducted in support of the objective of providing natural history data including cognitive, behavior, motor progression and insights into the neurobiology of HD. Individual sub-study proposals will develop data analysis plans specific to the objectives of each sub-study. Qualified researchers can apply for and obtain access to the anonymised Enroll-HD data to perform additional exploratory or data mining analyses. If necessary, investigators may request guidance for development and implementation of statistical analyses from the Enroll-HD Steering Committee.

## **7 STUDY MANAGEMENT**

### **7.1 Participants Lost To Follow-Up**

For participants who are not seen 6 months after a regularly scheduled annual visit, the site will attempt to contact the participant to determine if the lack of response is health related and to determine the health status of the participant. The site staff will make 3 attempts to contact the participant within a period of 3 months. Each attempt will be made once a month and at different times of the day (if possible, sites are encouraged to attempt contact more frequently). Participants are considered lost to follow up if all 3 attempts fail. For these participants, where applicable, vital status registries e.g., National Death Index in the United States, will be screened to obtain vital status information. Based on the information obtained, a final disposition of the participant will be entered into the eCRF. The informed consent process and forms outline these procedures. Any data and bio-samples collected prior to loss to follow up will be available for inclusion in all analyses.

### **7.2 Data Entry/Electronic Data Capture System**

The data are entered electronically via secure internet-based technology. Access to the eCRFs is limited by password and can only be granted by the study administrator after authorization of the Steering Committee. Any given site investigator in Enroll-HD can only see data on participants from their site. The data managers who are responsible for the data quality and integrity have access to all sites' data. Clinical research monitors, who are responsible for monitoring data for site that are assigned, can only review the data from those sites. They are responsible for study monitoring and ensuring compliance with the study protocol.

### **7.3 Source Documents**

The investigator should maintain source documents for each participant enrolled in the study. Source documents such as participant charts and doctors' notes will be kept as part of the participants' medical records. For participants who do not have a medical record per se, another method of documentation and record keeping will be employed. Participant files including medical records and signed participant ICFs must be available for review in the event the site is selected for monitoring, audits, or inspections.

## **7.4 Quality Assurance and Monitoring**

To obtain optimal data quality and reach the highest standards of reliability, Enroll-HD is monitored on the basis of the principles of Good Clinical Practice (GCP) according to International Conference on Harmonisation (ICH) guidelines:

- a. The rights and well-being of human participants are protected.
- b. The reported data are accurate, complete and verifiable from source data.
- c. The conduct of the trial is in compliance with the currently approved protocol/amendments and the applicable regulatory requirements.

Quality assurance (QA) refers to the procedures put in place to ensure quality, whereas quality control (QC) refers to the evaluation of the effectiveness of those procedures. The key distinction is between preparing for quality in the study (QA) and checking for quality of data collected (QC). Investigators' meetings, training and extensive written guidelines and SOPs and help texts and plausibility checks built into the eCRFs are put in place to ensure appropriate conduct of the study.

QC will be handled by data monitors who visit sites to ensure that procedures are being followed, including checking on-site assessments, giving feedback to sites and ensuring up-to-date training and accreditation. Central checking of data for completeness and plausibility at the level of the data repository will also be employed. Sites are monitored at least annually to check source documents (i.e., informed consent, date of birth, gender, medical history, genetic test results).

Enroll-HD has defined a monitoring plan and SOPs, which include guidelines for the conduct of high quality epidemiological research. The monitoring plan details the data monitoring process by defining key information regarding eCRF completion, source data verification, study procedures and the data flow process.

## **7.5 HD Identification Number (HDID)**

Before participant data are entered, a unique HD Identification Number (HDID) for each participant is created via a web portal, based on unchanging information (date of birth, birth name, place of birth and mother's maiden name). The HDID is a nine-digit number created by a secure one-way algorithm. The identifying data are used for the split second needed by the algorithm needed to generate the HDID and are never stored electronically on the web portal or in the study database. The investigator must store the original data and the HDID in the source documents (participant file) and in the investigator file.

## **7.6 Data storage and security**

Initially the internet-based application and the study database will be physically housed at the University of Ulm, the current host of the REGISTRY study. It is anticipated that the application and database will be migrated to a co-location facility that meets SAS70 Type II compliance or equivalent. This criterion requires that the facility will have redundant, full Uninterruptable Power Supply (UPS) and a backup generator, as well as appropriate HVAC (Heating, Ventilation, and Air Conditioning) and fire/flood protection systems. Additionally, the co-location facility will be appropriately secured with multiple levels of security and be manned continuously. The co-location agreement will require appropriate Service Levels that will meet the requirements for the Enroll-HD study. These will include, but will not be limited to, access to the internet, backup and restore policies, uptime, mean time to repair, disaster recovery, and business continuity. These requirements are needed to ensure the appropriate level of security, data protection and data access.

All accounts are password protected. Permissions are carefully maintained to allow only the required level of access to study data. The operating environment requires username/password authentication, and implements its own permissions structure at the file system level based on user ID and group ID. Files and directories are carefully set with only the required level of access. User ID's are required to change password on a regular basis.

Systems maintained by Enroll-HD and its partners (Outcome Sciences, 2MTand BioRep), adhere to approved standards for the security of health information and are compliant with 21 CFR Part 11, EU Directive 95/46/EC, and International Safe Harbor Privacy Principles.

## **7.7 Data Management**

Each participating site will receive appropriate training, which describes all processes required for a clinic to become a study site, enrolling participants, providing follow-up data on enrolled participants, maintaining study documents or files, reporting adverse events, and closing the study. All site staff who participate in enrolling participants, collecting or entering data for the study will be required to undergo appropriate training. A data management plan will be created and will describe all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs will include programmable edits to obtain immediate feedback if data are missing, out of range, illogical, or potentially erroneous. Concurrent manual data review will be performed

based on parameters dictated by the plan. Ad hoc queries will be generated within the EDC system and followed up for resolution.

Qualified researchers may request de-identified data and bio-specimens from the Enroll-HD study. Detailed procedures will be available on the Enroll-HD web portal regarding the submission, review, approval and processing of such requests. All requests will be reviewed to ensure the qualifications of the investigator, conformity with participant informed consent and to provide scientific advice. Requests for non-replaceable biospecimens will require an additional level of review. Any transfer of biospecimens will adhere to all applicable local ethics regulations. A general description of all projects will be posted on the Enroll-HD website and investigators who receive clinical information and/or biological samples will be asked to return all raw data for use by the research community.

## **7.8 Changes to the Protocol**

Any substantive modifications of the study protocol will require a formal amendment. Protocol amendments will not be implemented until they are reviewed and approved by the IRB/EC. Investigators must adhere to the study protocol and any major deviations from the protocol are prohibited unless they are preceded by an amendment and approval of the Enroll-HD Steering Committee.

## **7.9 Study Governance**

The Enroll-HD study is funded by the CHDI Foundation, Inc. The Funding Organization along with the advice of the Principal Investigator will select qualified physicians, scientists and members of the HD community to serve on the Enroll-HD Steering Committee.

The Enroll-HD Steering Committee is responsible for overseeing the conduct of the study. The Steering Committee will be responsible for the following:

- Overall safety and protection of research participants.
- Overseeing the systems that protect the privacy and confidentiality of the research participants.
- Ensuring data integrity and quality.
- Overseeing data sharing and publication policies.
- Reviewing and approving any changes to the protocol or inclusion of sub-studies and/or ancillary studies.

The Steering Committee may form committees made up of qualified individuals to assist with carrying out the management and oversight of the study. In addition, a CRO will be contracted by the Funding Organization to carry out the overall operational management of the study. This includes data monitoring and site management and coordination. The CRO will work with the regional investigator networks to ensure the smooth operational execution of the study. The overall responsibilities of the CRO are detailed in a separate agreement.

### **7.10 Publication Policy**

The Enroll-HD study supports the use the International Committee of Medical Journal Editors (ICMJE) guidelines for authorship ([www.icmje.org/ethical\\_1author.html](http://www.icmje.org/ethical_1author.html)) of publications that describe analyses of clinical data or bio-specimens collected within Enroll-HD (Enroll-HD Publications); these criteria are also appropriate for journals that distinguish authors from other contributors.

For other than baseline Enroll-HD publications, the persons responsible for study conception, design, and analysis, as well as the site investigators who recruited the research participants whose clinical data or bio-specimens are analyzed in the Enroll-HD publication, will be offered the opportunity to meet the criteria for authorship. Site investigator authors will be listed in descending order of number of research participants.

As a courtesy, all persons to be named as authors of an Enroll-HD publication are expected to respond to requests regarding the publication in a timely manner to ensure prompt dissemination of data. If a reply is not received within a reasonable period of time the lead author may decide to go forward without the author's input.

Enroll-HD publications must acknowledge the contributions of the Enroll-HD investigators and other key center staff that participated in the collection of the data and specimens. The following definitions will be used to assign appropriate acknowledgement:

Co-Investigator/Collaborator: A person who does not meet the criteria for authorship of the study, but who acted as an investigator or study coordinator for Enroll-HD. Co-Investigators may be listed in the appendix (or online – depending on the journal) and are indexed in PubMed. This will include a listing of Co-Investigators/Collaborators under the name “The Enroll-HD Study Group”; this name will be included on the authorship line. The number of individuals each site is permitted to include on the list for “The Enroll-HD Study Group” will be

proportionate to the number of subjects recruited at their site. This number will be determined and approved by the Enroll-HD Steering Committee.

Contributor: A person who does not meet the criteria for authorship, but has contributed in other ways, including collection of data; technical help; acquisition of funding; supervision of key personnel; contribution of drugs, reagents, equipment or patients; or editing the manuscript for non-intellectual content. Contributors are listed in the Acknowledgement section of the manuscript.

To the extent possible, names and centers should be listed for online review and appropriate indexing. “The Enroll-HD Study Group” listing may be obtained from the Enroll-HD Steering Committee or a committee delegated with responsibility. The Steering Committee will also delegate responsibility for maintaining the Investigator List and will periodically review the listing for accuracy. If there are any disputes in respect to authorship of a publication or the Investigator Listing the Steering Committee is responsible for resolving the issue.

Enroll-HD publications must also acknowledge, as a class, the research participants in the study. The CHDI Foundation, Inc. and other entities providing financial support for the Enroll-HD study must be acknowledged as such.

For sub-studies and ancillary studies, members of the sub-study team and the co-investigators/collaborators will be given one year after the end of the study to publish the major conclusions; after this period the data will be released for data sharing.

## **8 ETHICAL AND REGULATORY CONSIDERATIONS**

### **8.1 Participant Confidentiality**

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing participant data. By signing the protocol, the institution and/or investigator commit to complying with all related applicable international and local laws and regulations as well as any applicable Safe Harbor privacy principles.

There are several provisions in place to maintain integrity, confidentiality, and security of participant information. Data are stored using a code or a participant identification number (HDID) with no identifying information. Researchers and other users only have access to completely de-identified data. The Enroll-HD servers are managed by full-time system administrators. All network traffic is encrypted via network hubs to minimize 'eavesdropping' attacks. All computers run virus protection software full-time and are updated with the latest virus detection strings regularly. Servers are customized to run the bare minimum of network services in order to minimize potential 'back door' attacks, and are updated on a regular basis with the latest vendor recommended software fixes. The system is backed up on a daily basis and mirrored by a second server in a similarly protected environment located at a physically distant (>50 km) site. All CRF data and other critical study data are fully audit trail-enabled so that all changes to the data can be monitored and/or recovered.

All accounts are password protected. Permissions are carefully maintained to allow only the required level of access to study data. The operating environment requires username/password authentication, and implements its own permissions structure at the file system level based on user ID and group ID. Files and directories are carefully set with only the required level of access. User ID's are required to change password on a regular basis.

Finally, biospecimens are de-identified for storage and the central repository will never have access to identifying data.

### **8.2 Data Safety Monitoring Committee (DSMC)**

The Enroll-HD DSMC will consist of a minimum of five independent members not connected with the study; membership will include a practicing clinician, a biostatistician, a psychiatrist, a geneticist or genetic counselor and a medically trained individual from an HD family. The DSMC will be nominated by Enroll-HD Steering Committee and will meet via telephone conference on a quarterly basis and may hold face-to-face meetings as deemed appropriate. The DSMC will periodically review coded

data from the Enroll-HD study for potential safety concerns including: (1) Analyze and categorize the occurrence of reportable events (ref. Section 5.2) (2) Develop and recommend policies related to these events; (3) Review discrepancies between research and diagnostic genotyping and monitor the quality of the research genotyping procedures. The DSMC will report its findings and recommendations to the Steering Committee.

### **8.3 Institutional Review Board/Independent Ethics Committee**

IRB/IEC approval consistent with local regulations will be obtained for each site. Prior to enrollment of potential participants at a given site, the study protocol will be submitted together with its associated documents (e.g., Informed Consent Form (ICF), questionnaires, and communication materials) to the responsible IEC for its review. The written favorable opinion/approval of the IEC will be provided to each study physician, and a copy will be filed in the Study Master File. Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IRB/IEC in a manner consistent with local regulations. Pertinent safety information will be submitted to the relevant IRB/IECs during the course of the study in accordance with local regulations and requirements.

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## **10 APPENDICES**

### **10.1 Summary of Enroll-HD Sub-Studies**

#### **10.1.1 Pre-motor manifest HD**

**BACKGROUND:** Early, sensitive measures of disease progression in pre-motor manifest expansion mutation carriers will support the scientific and economic feasibility of future therapeutic trials, particularly in this population.

**AIMS:** To implement validated clinical outcome measures that are sensitive to detecting and tracking very early changes in HD. Assessments and outcome measures will be selected based on longitudinal data from TRACK-HD and PREDICT-HD (both prospective, multi-national studies aimed at identifying sensitive reliable outcome measures of HD in the very early stages of the disease).

**STUDY POPULATION:** All participants have been tested for the CAG mutation expansion.

**ASSESSMENT:** The assessment battery will be guided by the longitudinal data from TRACK-HD and PREDICT-HD. The battery is likely to include measures of quantitative motor, cognitive, behavioural domains, imaging (MR-based: IRB/ERB approvals for this component would be sought under a separate project approval), and biological samples (e.g. blood).

**ASSESSMENT DURATION:** 45-60 mins (excluding imaging component).

**METHODOLOGICAL APPROACH:** The development of the pre-motor manifest HD battery is based on a data-driven decision founded on the results from large scale, multinational, multicentre longitudinal studies to detect biomarkers of disease onset in pre-motor manifest HD carriers (TRACK-HD and PREDICT-HD). This sub-study will extract tasks with the highest proven sensitivity for detecting onset and progression of very subtle changes that occur in the very early stages of HD (no overt motor signs, TMS  $\leq 5$ ). Changes/modifications to the recommended scales/assessments will be reanalysed until a finalized assessment battery has been agreed for inclusion into Enroll-HD.

There are three main objectives within this sub-study, 1) to incorporate into Enroll-HD a modified, shortened pre-motor manifest HD assessment battery of tasks that seem highly promising as biomarkers of disease onset in this population, and 2) to field test this assessment battery in the Enroll-HD population to establish the robustness of the test

battery, and 3) to establish the reliability and sensitivity of these tasks in languages used in Enroll-HD.

Therefore, the Enroll-HD study is constrained by the fact that it will only be possible to provide equipment associated with high costs to a restricted number of study sites (for example, quantitative motor assessment will be coordination within sites where equipment is already in situ). This cost issue also applies but to a lesser extent for the computerised cognitive assessments. Therefore, the pre-motor manifest assessment battery will incorporate two versions: 1) a brief (paper and pencil, interview-based, clinical rating scales) and 2) extended (quantitative motor, computerised cognitive) assessment protocol.

Necessary data on languages other than the languages already tested in TRACK-HD and PREDICT-HD (Castilian, Dutch, French, English, German), will be used to determine whether these assessments are reliable and sensitive in other languages.

OUTCOMES: The goal of harvesting these data is to 1) replicate the findings from TRACK-HD and PREDICT-HD, and 2) analyse results according to country to identify any country or culturally dependent changes, and 3) demonstrate that these translated versions of the assessments result in similar observations independent of the language used for the study.

At this stage, it will be important to make sure we can prepare the assessments in the various languages used in Enroll-HD, replicate the results obtained in PREDICT-HD and TRACK-HD. PREDICT-HD and TRACK-HD data are obtained in rigorously controlled study conditions according to standards typically applied to clinical trials. Therefore, it will be important to address whether the proposed premanifest HD battery retains its sensitivity and reliability when there are lower levels of scrutiny and quality control.

By obtaining these data it will be possible to:

- Explore whether the results can be used to derive clinically meaningful results (e.g., to inform a clinician about a patient's competence and capacity to continue their job).
- Consider how far pre-motor manifest HD participants differ from the control population database (referring to TRACK-HD database).
- Propose a longitudinal arm to data collection to further validate findings in PREDICT-HD and TRACK-HD.

In conclusion, this sub-study will field test the assessments developed by TRACK-HD / PREDICT-HD to demonstrate that these assessments retain sensitivity as reliable

biomarkers independent of cultural/language differences and to establish validated versions in the languages used within the Enroll-HD study.

### **10.1.2 Advanced stage HD**

**BACKGROUND:** The UHDRS does not allow a meaningful assessment for the advanced stages of HD for a number of reasons. For example, the standard UHDRS cognitive assessment consisting of timed psychomotor tasks, cannot be administered to people in more advanced stages of HD due to their motor impairment and dysarthria. Therefore, an important component of the cognitive phenotype is very often not assessed in the advanced stage HD participants. Likewise, communication impairments preclude an interview-based behavioural assessment. Lastly, the motor phenotype for all items of the motor scale, requiring active participation by the participant is not informative in more advanced stages. Other aspects like impaired mobility and control over bodily functions that contribute greatly to the caregiver burden and the medical needs of advanced stages of HD are not captured in the standard UHDRS assessment. Therefore this sub-study proposes an assessment of advanced stage HD based on the pioneering scale development lead by the sub-study team.

**AIM:** To validate a novel scale called “Advanced-stage UHDRS” for use in clinical and research practices.

**STUDY POPULATION:** Enroll-HD participants with a Total Functional Capacity score of  $\leq 5$  (includes Stage III) and a reduced independence scale score of  $< 70\%$  .

**ASSESSMENT:** The Advanced-HD scale consists of four components: motor function, somatic domain, cognitive assessment and behavioural assessment.

**ASSESSMENT DURATION:** 30 minutes

**METHODOLOGICAL APPROACH:** Trained raters will administer the Advanced-HD scale in addition to the standard UHDRS. Participants will be selected based on TFC score of  $\leq 5$ . The population sample will be stratified according to each scale point on the TFC from 0 to 5. The study aims to recruit a total of 120 advanced stage HD patients. Participants undergo at least two assessments at 1 year interval ( $\pm 2$ months). The Advanced-HD scale will be assessed with the standard UHDRS. The first phase of this study will be coordinated in three countries.

**OUTCOMES:** The objective is to determine whether the Advanced-HD scale is useful at each of the TFC scores below or equal to 5. The main objective is to compare the

capacity of both Advanced-HD scale and standard UHDRS to assess the progression of the disease at one year. Once the Advanced-HD scale has been validated and, if necessary, the inclusion criteria have been refined, a second phase will assess the performance of the Advanced-HD scale between languages.

### **10.1.3 Juvenile-onset HD**

**BACKGROUND:** In approximately 5% of cases, the onset of symptoms may occur before the age of 20 years, and this is called Juvenile-onset HD (JD). The clinical presentation of JD can be strikingly different from that of adult-onset HD. In young people affected by JD, and particularly in those with onset in the first decade, there is a dominant clinical picture of bradykinesia, rigidity and dystonia. They are also more likely to develop epilepsy. This distinct JD phenotype is not captured completely by the items of the current version of UHDRS, which was originally developed to assess the most prevalent phenotype which is the adult onset of the disease. Therefore, for patients with Juvenile HD, a modified version of the motor section of the UHDRS will be used alongside the existing motor section so that new items which may be more appropriate to the clinical presentation seen in JD can be evaluated. To ensure that a complete picture of the neurological symptoms of JD is gained, a standard full neurological examination appropriate to age will be carried out and recorded. In addition, parent/guardians of those affected by JD will be invited to record symptoms and details of any symptomatic treatments being used in a diary. This additional information will allow us to observe the progression of symptoms in JD and also allow us to gain a better understanding of the usefulness of different treatments in managing these symptoms.

#### **AIMS:**

- a. To assess the reliability and validity of the JD assessment to track the onset and progression of this rare phenotype. To construct new rating scales based on an iterative process.
- b. To monitor the progression of symptoms and signs of those affected by JD using modified UHDRS scales of motor and function (functional assessment, TFC). This will provide some basic data to analyse the usefulness of the proposed rating scales.
- c. Caregivers of those affected by JD will be invited to record both symptoms experienced by the person with JD and details of any symptomatic treatment being used in a diary. This will allow us to observe the progression of symptoms in JHD and also allow us to gain a better understanding of the usefulness of different treatments in managing these symptoms.
- d. There may be significant delays in diagnosis especially if the young person presents with behavioural problems. Caregivers will be asked questions to capture the

number of contacts with professionals in the time between onset of concerns about the young person and the confirmation of diagnosis.

- e. To undertake a qualitative study of the issues experienced by young people and caregivers in order to develop new rating scales which assess relevant aspects of the phenotype. Not all aspects can be undertaken but in depth interviews will take place if pain is a specific feature of the condition for an individual.

**STUDY POPULATION:** Enroll-HD participants with JD (motor onset aged 20 or younger).

**ASSESSMENT:**

- a. UHDRS JD Motor Assessment
- b. UHDRS JD Functional Assessment (including JD functional scale and JD total functional capacity scale)
- c. Diagnosis questions (brief questionnaire relating to the process of diagnosis). This data will only be collected at the first baseline visit.
- d. Standard full neurological examination appropriate to the age of the individual being assessed will also be carried out to identify any other possible signs of JD.
- e. Diary to help caregivers monitor medication and symptoms on an ongoing basis.
- f. Two-three patients who are willing will be invited to participate in a video of the motor examination to facilitate consistency of data capture as part of a wider international collaboration.
- g. Five in depth taped interviews will be undertaken to explore carers perception of pain. The interviews will be semi-structured and undertaken by a psychologist with experience of qualitative work and analysed using Interpretative Phenomenological Analysis. The aim is to inform the development of questions about pain as feature of JD and builds on a previous collaboration (1).

**ASSESSMENT DURATION:** 45 minutes. Diary entries (paper based or online) would be completed whenever symptoms and changes to medication were noted by the caregiver.

**METHODOLOGICAL APPROACH:** Some patients with JD are already being seen as part of the Enroll-HD project and so the additional data can be accommodated as part of the Enroll-HD study visit. Other patients may not attend the clinics but families identified from paediatric neurologists or the patients' organizations will be given the option of being seen at home by the research assistant who will be trained in the following assessments. Data will be collected and analysed after 6 months to ensure that no further changes need to be made to the diary format / instructions.

OUTCOMES: Data will be collected from 30 JD patients and subjected to a Rasch analysis which will give a guide to the performance of the rating scales and aid further refinement. N = 30 has been determined from both empirical and simulation Rasch analysis studies as the minimum number required to produce useful items to move forward to larger more definitive studies.

Historically, scale development and evaluation involved large samples of people. These are costly, time consuming and, in the case of JD, not easy. Rasch analysis lends itself to smaller sample work for two reasons. First, an inherent mathematical feature of the model is parameter separation. That is, the estimates of item parameters are independent of the sampling distribution of the persons. Likewise the estimates of person parameters are independent of the sampling distribution of the items.

Methodology for statistical analysis will follow Rasch analysis using statistical package RUMM2020. The parameterization is maximum likelihood method.

Basic analyses undertaken within the Rasch measurement framework include, but are not limited to, an examination of:

- a. targeting of person measurements to item threshold locations
- b. ordering of category threshold locations, and category probability curves
- c. threshold probability curves
- d. threshold map
- e. distribution and ordering of item locations
- f. statistical (overall chi sq, item fit residuals, item chi square probability) and graphical (item characteristic curves) fit indicators
- g. residual correlations
- h. differential item functioning
- i. scale information function
- j. person separation index
- k. person fit
- l. relationship between raw scores and interval measurements

#### **10.1.4 Frontal behaviours (FrSBe, Irritability and Apathy)**

**BACKGROUND:** Standard clinical assessments used to capture neuropsychiatric features of HD (the UHDRS Behaviour and Problem Behaviour Assessment-Short) are interview-based rating scales conducted by a trained rater with the patient, and when available, the companion/caregiver. These assessments provide an overall impression of the frequency and severity of key neuropsychiatric problems over a period of 4 weeks prior to the interview. Whilst these rating scales are sufficient in identifying a clinical problem, there is a clear need to identify robust clinical outcome measures of *specific* psychiatric features to inform clinical practice and provide a reference point for future trials of new treatments as they are developed. This sub-study proposes to test the suitability of existing measures of frontal behaviours, in particular apathy and irritability, to a large HD population in order to derive appropriate sub-scales that can be used in clinical intervention. These preliminary data are required to inform power calculations for future clinical trials aimed at modifying symptom frequency and severity.

#### **AIMS:**

##### **Primary aims:**

- a. To determine the reliability and validity of frontal behaviour measures, both patient, informant and rater versions
- b. To investigate the differences in patient and informant based assessment methods
- c. To better understand frontal-type behaviours in HD

##### **Secondary aims**

- a. To investigate the association between the outcome measures and various demographic and clinical characteristics
- b. To investigate the association between the outcome measures and the other neuropsychiatric scales (e.g. PBA-s, UHDRS behaviour, HADS-SIS)

**STUDY POPULATION:** Confirmed HD gene mutation carriers (Pre-HD, Stages I to III), aged 18 years and older

#### **ASSESSMENT BATTERY:**

- a. Irritability component of Apathy and Irritability Scale (2); patient, informant and rater versions
- b. Irritability Scale for HD (ISHD); Companion diary entries, once per day for 7 consecutive days
- c. Apathy Scale; patient, informant and rater versions.

- d. Frontal Systems Behaviour Scale (FrSBe; participant and informant versions)

ASSESSMENT DURATION: 45 minutes each for patient and companion. 20 minutes for rater.

METHODOLOGICAL APPROACH: The first phase will coordinate study sites across three countries. An estimated 300 participants recruited from different stages of the disease will be enrolled into the study (100 participants in total per country; 50 Pre-HD, 25 Stage I, 25 Stage II and 25 Stage III).

For rater-based questionnaires, a small pilot design will be used to determine a learning effect for raters who are new to these scales. Comparisons will be run using first 10 participants per study site.

Test-retest reliability will require approximately 170 participants across languages, with a follow-up assessment after 14 days (+/- 7 days). For the Irritability Scale (HD), which follows a 7-day diary format, test-retest reliability will take diary entries completed over 14 consecutive days. Comparisons will be made between entries recorded in week 1 compared to week 2.

For rater based versions of scales, it will be important to assess inter-rater reliability (n=25 per language area). Two raters should complete ratings at the same time during the clinical interview. If it is not possible to have a second rater present during the interview, then videoed interviews (with written participant consent) will be recommended.

Healthy normal participants will be recruited in order to demonstrate that these translated versions of the assessments result in similar observations independent of the language used for the study.

OUTCOMES: There will be several main outcomes from this sub-study. Importantly, these the preliminary data will inform power calculations for subsequent interventional trials. In addition, it will provide data to understand more fully the nature and course of frontal-type behaviours in HD. These data will help identify whether scales are sensitive in HD and at which stages.

The outcome of this sub-study will guide the suitability of these existing measures of frontal behaviours, in particular apathy and irritability, as clinical outcome tools for use in interventional trials in particular open-label efficacy trials.

It will also be important to combine the items included in all of the rating scales and look at the psychometric properties. This would inform about whether each item contributes

unique extra value compared to the other items. It would also be important to explore how each independent item performs relative to others in terms of Item Response Theory methods (IRT).

### **10.1.5 Linguistic abilities**

**BACKGROUND:** HD has several typical cognitive deficits, including executive dysfunction (poor planning and organizational behaviours) and memory (impaired free recall of items). There have also been reports of language disorders in the disease, which assume a typically 'frontal' phenotype (poor verbal fluency and impaired syntactic abilities), possibly reflecting the fronto-striatal pathology associated with the disease. However, conflicting evidence from the few studies that have investigated this area make it unable to determine whether the impact of the subcortical damage caused by HD is related to dysfunction in language processing. Using more specific and sensitive tools than those classically used in aphasia evaluation, HD patients show impairments in language processing and more specifically in syntactic processing (3).

**AIM:** To demonstrate that syntactic assessment is a useful tool for longitudinal follow-up in HD and thus might be helpful in therapeutic trials. It may also discriminate between premanifest HD and controls.

**STUDY POPULATION:** HD gene mutation carriers, Pre-HD and early HD (Stage I).

**ASSESSMENT:** Sentence-Picture Matching Task (SPMT): 42 sentences

**ASSESSMENT DURATION:** 10 minutes

**METHODOLOGICAL APPROACH:** This study is designed to achieve the following objectives: to obtain clinical data on a sample of early HD patients and control participants and to characterize the nature of language impairment in these samples of HD patients.

The SPMT will be administered to 20 Pre-HD participants (Total Motor Score,  $\leq 5$ ), 20 early stage HD participants (Stage I, TFC 10-13) and 30 control participants (matched for age and education to HD groups) from each country participating in the study.

Longitudinal data will be collected following a one year interval, not more than two months apart from a full Enroll-HD evaluation to be able to extract the clinical characteristics of the patients.

OUTCOMES: Syntactic abilities using the SPMT in this population sample will be explored using ANOVAs with SPMT accuracy as the dependent variable and as independent variables: group (HD Stage I, Pre-HD and controls) as a between-subjects factor and canonicity (canonical and non-canonical sentences) and plausibility (plausible vs. non plausible) as within-subject factors. In addition, SPMT accuracy scores will be correlated with other scales assessing the evolution of the disease and the demographic characteristics (as covariates).

### **10.1.6 Validation of the Montreal Cognitive Assessment (MoCA) General Cognitive Impairment**

BACKGROUND: As clinical trials to assess the efficacy of so called ‘cognitive enhancers’ are likely to be developed in the near future, it is worthwhile to validate the Montreal Cognitive Assessment (MoCA) as a tool for detecting ‘global’ cognitive change in HD that might not be evident in scores on those tasks currently included in the Enroll-HD protocol.

AIM: To investigate cross-sectional and longitudinal sensitivity of the MoCA to cognitive change in different stages of HD, including premanifest HD. Additionally the test-retest reliability will be investigated. The inclusion of non-HD gene carriers will permit the collection of normative data on this task.

STUDY POPULATION: Confirmed HD mutation carriers of all stages of the disease including premanifest-HD.

ASSESSMENT: MoCA, rater administrated.

ASSESSMENT DURATION: 5-10 minutes

METHODOLOGICAL APPROACH: In order to investigate the cross sectional and longitudinal sensitivity of the MoCA, as well as the test re-test reliability participants will be stratified according to six groups; gene-negative controls, Pre-HD individuals (TFC =13, TMS ≤ 5), and individuals in the early (Stage I), mild (Stage II), moderate (Stage III) and severe (Stage IV) stages of HD.

Population sample size: 50 non-mutation gene carriers, 100 pre- HD gene carriers, 100 HD Stage I, 50 HD Stages II and III, and 25 HD Stage IV.

The study will follow semi-randomised design. Study sites should commit to pre-specified “packages” for data collection. Two packages are offered: a) to include four

participants in Stage I, two participants in each Stage II and III, and one participant in Stage IV; b) includes one control non-gene carrier and two pre-motor manifest HD gene carriers.

Once these data are collected, they will be used to guide towards further refined aims, such additional stratification according to demographic variables as age and education, and language.

To determine the longitudinal sensitivity of this measure, the same procedure will be followed, where participants will be followed up one year later.

The test re-test reliability of the MoCA will be determined following the same procedure for a smaller number of individuals in each stage, after an interval of one month. This will require 40 Stage I, 20 Stage II, 20 Stage III and 10 Stage IV participants. Primary outcomes will involve indices of sensitivity (0.9) – specificity (0.85) of the MoCA within the HD population (stages I–IV and pre-motor manifest HD gene carriers) and healthy control participants. Additionally re-test reliability measures will be obtained within these population samples.

**OUTCOMES:** This study will seek to examine the use of the MoCA as a tool for detecting and tracking ‘global’ cognitive change in HD that might not be evident in scores on those tasks currently included in the Enroll-HD protocol.

### **10.1.7 Tapping**

**BACKGROUND:** Performance of individuals with HD on finger or hand tapping tasks is shown to be highly correlated with various indices of disease severity and is a sensitive marker of change over time (4). Additionally, measures of tapping performance are strongly related to estimated-years-to-onset in pre-motor manifest HD (5).

**AIM:** To investigate cross-sectional and longitudinal sensitivity of a finger/hand-tapping task, as a measure of cognitive change across different stages of HD, including pre-motor manifest HD.

**STUDY POPULATION:** Confirmed HD mutation carriers of all stages of the disease, including Pre-HD.

**ASSESSMENT BATTERY:** Task selection and device will be determined following systematic review of all tapping tasks so far employed in HD. The task will measure motor speed, dexterity and psychomotor speed.

**ASSESSMENT:** approximately 5 minutes

**METHODOLOGICAL APPROACH:** This device and task instructions will be distributed to multiple study sites and should be administered to confirmed HD gene mutation carriers of all stages of the disease.

**OUTCOMES:** Tapping performance appears to be a sensitive readout for both pre-motor manifest HD mutation carriers as well as manifest HD patients well into more advanced stages of HD. This sub-study will select a task with proven sensitivity to detect and track changes within HD across all stages will be tested for task robustness. These data will be use used specifically to assess task robustness within multiple study sites and confirm whether this device should be employed in the future, e.g. in the context of the Enroll-HD assessment battery and in the context of clinical trials.

#### **10.1.8 HD Quality of Life outcome measure (carer, patient)**

**BACKGROUND:** Previous work in health related quality of life in HD (6) shows that while generic instruments may be applied in HD patients, these may not fully capture the aspects of well-being affected specifically in HD. Generic instruments tend to demonstrate poor sensitivity to specific disease progression because they often fail to capture all aspects of well-being. Specifically, the SF-36 lacks items tapping into the relevant mood-related (7) and behavioural (8) aspects of Huntington's disease which affect health-related quality of life. The health-related quality of life (HrQoL) in HD is a new questionnaire meeting with psychometric standards and will be the first ever HD-specific quality of life instrument. This measure will enable the unique symptoms and consequences of this disorder on patients' everyday life to be formally ascertained and quantified, and will fill a long-standing practical gap in current clinical care and management of this disorder. An HD specific health-related quality of life questionnaire would therefore be extremely useful in understanding both the impact of disease progression and intervention on health status.

**AIM:** To develop and validate a patient-centred prototype questionnaire which examines health-related quality of life specifically in people with Huntington' disease, and to validate this instrument as an outcome measure to reflect a combination of factors: a person's health, symptoms, and level of physical and social functioning.

**STUDY POPULATION:** All Enroll-HD participants, including pre-manifest HD and at risk individuals.

ASSESSMENT:

- a. HD QoL: Self-rated by participant, and proxy-version completed by carer/companion
- b. Companion QoL survey
- c. EuroQuol 5, a non-specific quality of life questionnaire.

ASSESSMENT DURATION: 20 minutes each.

**METHODOLOGICAL APPROACH:** The development of the HD QoL scales falls into two stages. During Stage I (in progress and coordinated outside of Enroll-HD), data will be explored to gauge the suitability of conducting an exploratory factor analysis. It is anticipated that the majority of items will demonstrate a normal distribution using the Kalmogorof Smirnov test. The screened data will be factor analyzed to establish the underlying dimensions of the instrument. Principal components analysis (PCA) will be used and it is expected to find factors which can be clinically interpretable and to fall under the triad of underlying motor, cognitive and behavioural factors consistent with the typical presentation of HD. Any factors which appear clinically heterogeneous will undergo a further PCA to determine if there is a basis for establishing separate factors.

The psychometric characteristics of the factors will be examined including missing data, score distribution, summary scores, floor and ceiling effects, internal consistency (expressed as part-whole correlations between single items with the scale value) and reliability of the total scale (using Chronbach's alpha coefficient). The analyses of these data involve iterative changes to the questionnaire.

Once the HDQoL has been finalised, Stage 2 (the aim of this sub-study) will commence to establish the HDQoL as a valid, reliable and sensitive instrument in tracking the progression of disease. A target figure of 300 HD patients is required to participate in this validation study.

Patients will be asked to rate their duration of disease and their level of independence in daily life. Convergent validity can be determined by examining the correlations between the factors from the HDQoL instrument with other disease characteristics (such as functional motor impairment and cognitive status) and other QoL measures. Multivariate regression models can be used to examine the discriminative and evaluative properties of the HDQoL, as can known-groups validation.

In order to examine reliability of the instrument over time, after approximately 4 weeks from the receipt of the initial questionnaires, a second send-out will occur. Internal

consistency will be examined using Chronbach's alpha coefficient, and test-retest reliability using intraclass correlation coefficients.

In order to determine the sensitivity of the instrument to progression in disease state, a final send out of the HDQoL instrument (as per the initial Time 1 send out and post send-out interview) will be administered 12 to 18 months after the receipt of the initial questionnaire. Changes in HDQoL factors will be correlated with changes with motor, cognitive and behavioural disease symptoms. Standardized response means, effect sizes and ROC curves will also be used to determine sensitivity of the instrument.

Finally, in order to assist in interpreting scores over the progression of the disease, it would be important to determine minimally important changes i.e. the smallest (positive or negative) difference in scores that patients perceive as important. This will be done using anchor and distribution based methods.

#### **10.1.9 Physiotherapy outcome measures**

**BACKGROUND:** An evidence-based rationale for the development and evaluation of complex physiotherapy interventions is required to confirm the common perception that physiotherapy is beneficial in HD.

**AIM:** To evaluate a range of physiotherapy related outcome measures for use in future interventional studies.

**STUDY POPULATION:** Either a confirmed diagnosis of HD or HD gene mutation carrier.

#### **ASSESSMENT BATTERY:**

- a. The 6-Minute Walk test.
- b. The 10m Walk test
- c. The timed "Up and Go".
- d. Physical Performance Test
- e. Rivermead Mobility Index
- f. Barthel Index
- g. Berg Balance Scale
- h. Romberg and Sharpened Romberg Test
- i. Performance Oriented Mobility Assessment
- j. Four square step test
- k. International Physical Activity Questionnaire

**ASSESSMENT DURATION:** 60-90 minutes, two visits (one week apart). This study will be coordinated by the Physiotherapy Working Group Lead Facilitators.

**METHODOLOGICAL APPROACH:** Eighty participants with Huntington's disease; 20 pre-HD (TFC 13; no clinical signs of HD); 20 Stage I HD (TFC 10-13); 20 Stage II HD (TFC 7-9); 20 Stages III and IV (TFC 0-6). Twenty participants (tested twice) in each stage of disease would be sufficient to identify an intraclass correlation coefficient of .75, as well as a Pearson's correlation of .6 (two-tailed), with a power of 80% and an alpha of .05.

**OUTCOMES:** Reliability will be assessed using the Intra class correlation coefficient. Validity will be assessed using a Pearson's or Spearman's correlation coefficient correlating functional outcome measures with UHDRS Motor score and Functional Assessment scale for each subject. Minimal Detectable Change (MDC) will be calculated as  $1.96 * \sqrt{2} * SEM$  (standard error of measurement). SEM will be estimated by taking the square root of the mean error term from a repeated measures ANOVA. The MDC can be interpreted as the magnitude of change below which there is more than a 95% chance that no real change has occurred.

#### **10.1.10 Lifestyle factors**

**BACKGROUND:** HD mouse-model studies have shown that rearing mice in an enriched environment delays the onset of symptoms, raising the possibility that pre-symptomatic lifestyle may also affect age-at-onset in humans. Furthermore the age-at-onset of other neurodegenerative disorders such as Alzheimer and Parkinson diseases can be influenced by the type and level of activity regularly undertaken prior to the development of symptoms. A study conducted in Australia and New Zealand showed that avoiding a passive lifestyle may well delay the onset of symptoms of HD. Substantiating these findings may mean that at-risk individuals can be given lifestyle strategies, which if employed from an early age, may lead to symptoms developing several years later than would otherwise be the case.

**AIM:** To examine the link between lifestyle factors and the age at onset of Huntington's disease. The experience and outcome of this retrospective study will inform the development of a cross-sectional prospective study of lifestyle factors with a view to providing individuals at risk of HD with lifestyle strategies that may delay the onset of symptoms.

**STUDY POPULATION:** Manifest HD participants (Stages I and II).

**ASSESSMENT BATTERY:**

- a. Lifestyle Activity Questionnaire: Four sections (Education, Occupation & employment history, Interests & activities, Home duties & activities)
- b. Spirituality: Duke University Religion Index (DUKE)

ASSESSMENT DURATION: 30 minutes.

METHODOLOGICAL APPROACH: For this study a target number of 150-200 participants should provide ample power to detect the effects of a passive lifestyle on age at onset, but it may be possible to observe more subtle effects of intellectual or physical activity with increased numbers.

OUTCOMES: The study is aimed at detecting whether or not lifestyle activities (physical, intellectual and passive) have an impact on the age at onset of HD, independently of the effect of CAG repeat length, and to measure the size of any such impact in a different cohort.

Thirty leisure activities, classified as predominantly physical, intellectual or passive will contribute to total scores for each category of activity within each applicable life stage.

Lifetime average scores (i.e. leisure passivity, leisure intellectuality and leisure physicality scores) will then be generated by averaging the life-stage scores in each category over the nominal pre-morbid lifetime of each individual, defined as (age at onset - 13) years.

Non-leisure activity scores incorporate education, occupation and domestic activity data, again in the categories of physical, intellectual and passive activity. Lifetime average non-leisure scores are the sum of domestic, education and occupation scores within categories. Lifestyle scores comprise the sum of lifetime average leisure and non-leisure scores (within categories).

Relationships between age at onset, CAG repeat length and the various activity parameters will be examined using Pearson correlations followed by a series of linear regression analyses. Because of the known strength of association between CAG repeat length and age at onset, all regression analyses using activity measures as continuous variables will include CAG as a covariate. Where appropriate, different activity scores will be separately entered as variables into fully adjusted multiple logistic regression models. The criterion for significance of association is  $p < 0.05$ . Activity scores will be analysed across tertiles with the mean age at onset (with 95% CIs) calculated for each as a measure of the impact of activity on age at onset.

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