



Track-HD

Study Protocol

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Version 1.3

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Change Log

Date	Description of change(s)	Name
2007-06-20	Initial release	Lifer, S.
2007-06-24	Edits to blood sampling and processing, exclusion criteria, and clause in consent form regarding possible use of video and audio for research purposes.	Tabrizi S.
2007-06-28	Add gait assessment and Dutch and French IQ estimates and relevant references.	Stout J., Queller S.
2007-07-02	Revised consent forms per study sponsor's request.	Tabrizi S.



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2 Abbreviations

<u>Abbreviation</u>	<u>Definition</u>
ACD	Acid citrate dextrose
ADL	Activities of daily living
ANART	American national adult reading test
BBSI	Brain-boundary shift integral
C	Control
CAG	Cytosine-adenine-guanine
CRO	Commercial research organisation
CRF	Case Record/Report Form
CTMS	Clinical Trial Management System
DBC	Differential bias correction
DICOM	Digital imaging and communications in medicine
DNA	Deoxyribonucleic acid
DRC	Dementia Research Centre
DV	Dependent variables
eCRF	Electronic CRF
EBA	Evidence based assessment
EDTA	Ethylenediamine-tetraacetic acid
EHDN	European-HD Network
ELISA	Enzyme-linked immunosorbent assay
ES	Effect size
ETL	Echo train length
FAST	Fourier-acquired steady state
FHQ	Family History Questionnaire
FOV	Field of view
GE	General Electric
GRASS	Gradient-recalled acquisition in the steady state
HADS	Hospital anxiety and depression scale
HD	Huntington's Disease
HDNI	Huntington's Disease Neuroimaging Initiative
HSG	Huntington Study Group
HVLT	Hopkins verbal learning test
IA	Image analyst
ION	Institute of Neurology
IRB	Institutional review board
LB	Lymphoblastoid
LiHep	Lithium-heparin
LONI	Laboratory of Neuro Imaging
MIDAS	Medical image display and analysis software
MRI	Magnetic resonance imaging
NART	National adult reading test
NEX	Number of excitations
NHNN	National Hospital for Neurology and Neurosurgery
NIH	National Institutes for Health
NMR	Nuclear magnetic resonance department of ION
OCD	Obsessive-compulsive disorder
P	Psychologist
PI	Principal investigator
PM	Premanifest
QA	Quality assurance
QC	Quality control
QoL	Quality of life
QOLI	Quality Of Life Index
R&D	Research and development
RF	Research fellow



<u>Abbreviation</u>	<u>Definition</u>
RNA	Ribonucleic acid
RT	Reaction time
SBA	Short Behavioural Assessment
SD	Standard deviation
SDMT	Symbol digit modality test
SOP	Standard operating procedure
SPM	Statistical parametric mapping
SRB	Scientific review board
TE	Echo time
TFC	Total functional capacity
TIV	Total intracranial volume
TMT	Trail-making test
TR	Repetition time
UCL	University College London
UHDRS	Unified Huntington's Disease Rating Scale
VBM	Voxel-based morphometry
WASI	Wechsler abbreviated scale of intelligence

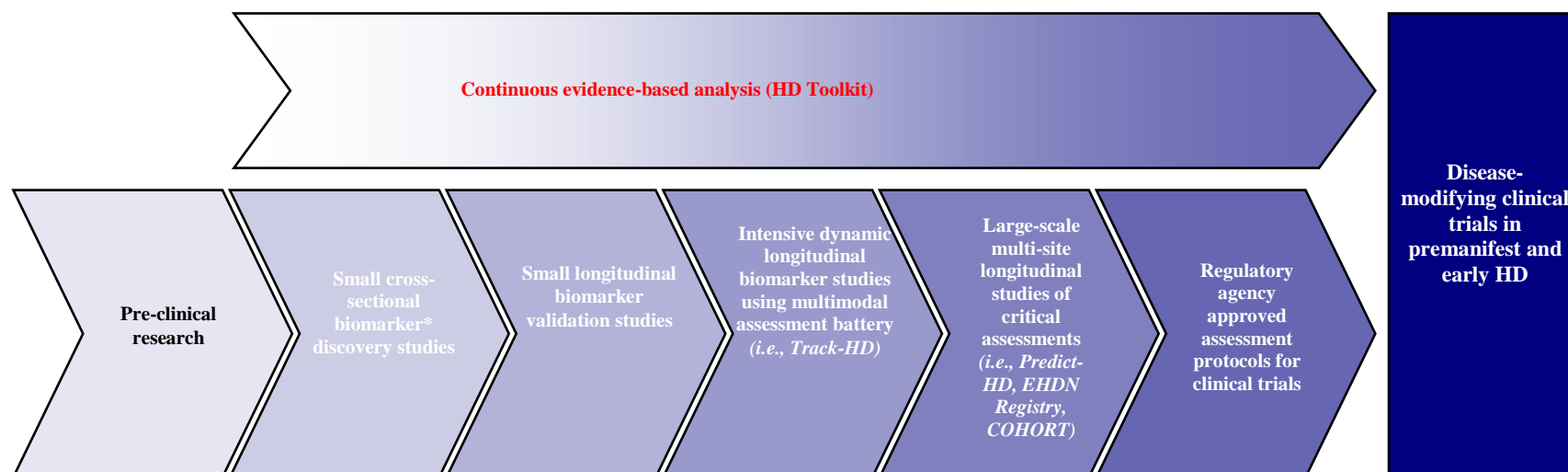


3 Executive Summary

Track-HD is a multi-centre, multi-national, prospective, observational biomarker study of pre-manifest and early Huntington's disease (HD) with a control group of volunteers not carrying the HD mutation. The goal of the project is to contribute essential methodology that will form the basis for neuroprotective trials in pre-manifest and early HD. Track-HD complements existing observational studies (e.g., Predict-HD, PHAROS, Registry, COHORT), sharing some features, such as the prospective longitudinal design, but also having areas of unique emphasis, including implementation of multi-site 3T MRI acquisition, and novel quantitative motor, cognitive, oculomotor, neuropsychiatric, and wet biomarker components. Another unique feature of Track HD is the use of only a small number of sites to allow greater flexibility for implementing relatively complex and expensive procedures and the possibility of greater flexibility for modifying study procedures as promising, new methods become available.

The protocol describes a study plan, including the study design, participant characteristics, measures, data management and analysis plans, study administration and coordination, a partial set of standard operating procedures, and plans for dissemination. Careful attention has been given to the rationale for the measurement approaches, and to the complementarities of Track-HD to similar ongoing studies such as Predict-HD.

Figure 1 provides a graphic representation of the clinical trial development pipeline, indicating our conceptualization of the role of Track-HD in this pipeline as building on pre-clinical research and small longitudinal biomarker studies, and in turn informing large-scale longitudinal biomarker studies which then are used to generate assessment protocols that are acceptable to regulatory agencies.



*Biomarker studies include imaging, cognitive, motor, oculomotor, behavioural, & laboratory biomarkers.

Figure 1 Clinical Trial Development Pipeline in HD

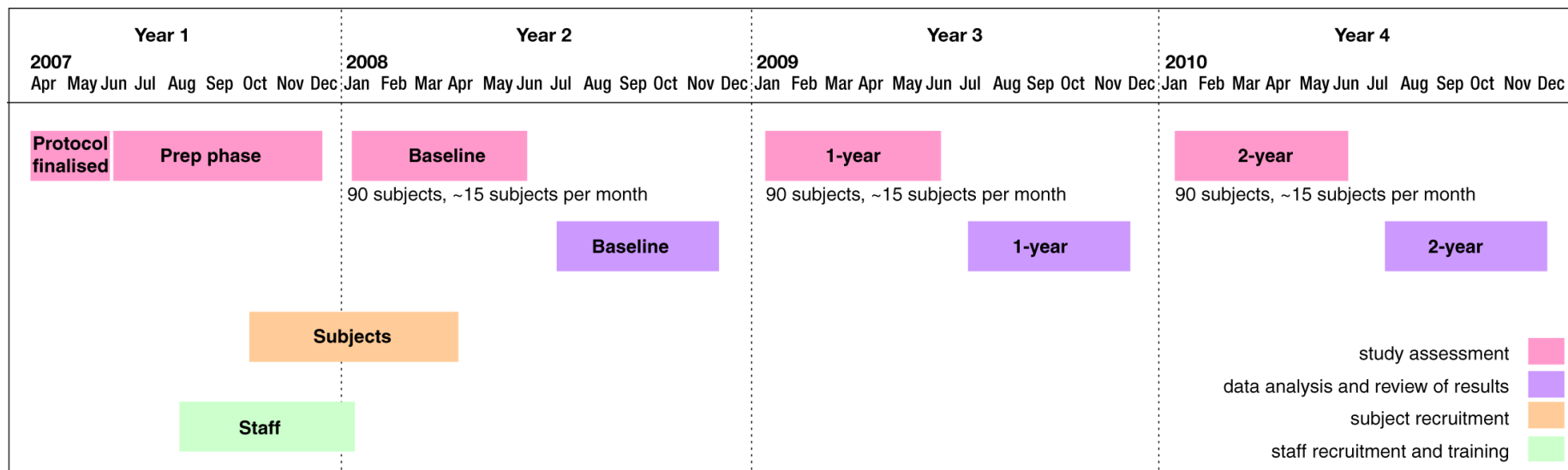


Figure 2 Generic timeline for Track-HD



3.1 Overall study design

The generic Track-HD study schedule is illustrated in Figure 2 and Table 1 summarizes the overall assessment plan.

	Visit 1 (baseline)		Visit 2 (12 months)		Visit 3 (24 months)
Subjects	90		90		90
Controls	30		30		30
Premanifest HD	30		30		30
Early HD	30		30		30
Pseudonymise	✓			Assess data to determine whether shorter interval useful	
Check criteria	✓				
Demographics	✓				
Biosamples	✓		✓		✓
Clinical/motor	✓		✓		✓
Neuropsychiatric	✓		✓		✓
Cognitive	✓		✓		✓
Quantitative motor	✓		✓		✓
MRI	✓		✓		✓
DNA/LB sample	✓				
Oculomotor	✓		✓		✓

Table 1 Overall assessment plan

3.2 Subjects overview

Each centre will recruit 90 subjects. The target cohort at each centre will be 30 control subjects, 30 premanifest (PM) HD expansion carriers and 30 subjects with early disease (stage 1 or 2). In order to increase the yield of disease-related changes in the premanifest cohort, a burden of pathology selection criterion will be used. Burden of pathology is given by $(CAG-35.5) \times \text{age}$. A threshold of >250 for the burden of pathology score has been set, which approximates to <15 years to estimated disease onset (calculations based on Predict-HD dataset by Doug Langbehn). Control subjects will be persons with normal repeat length and may be partners or spouses of premanifest subjects. Such individuals share environmental, genetic, social and dietary exposures as well as some psychological burden of living with HD. Further details on rationale for subject cohort are outlined in the main protocol.

4 Track-HD overview

4.1 Study title

Track-HD

4.2 Type of study

Multi-centre, multinational prospective observational biomarker study of carriers of the HD mutation either at the premanifest and early stages of HD along with non-carriers as controls with no experimental treatment.

4.3 Study centres

Data collection for Track-HD will begin in early January 2008.

The number of sites required will be influenced by ongoing sample size calculations based on analysis of study data. The first longitudinal one-year raw data cut from the full Track-HD cohort will be by July 2009 (data collected between January 2008 and June 2009).

The planned 4 study sites and site PIs include the following.

- Institute of Neurology, UCL, London
 - Sarah Tabrizi, MD, PhD (ST); PI of Track-HD
- University of British Columbia, Vancouver, Canada
 - Blair Leavitt, MD (BL)
- Université Pierre and Marie Curie, Paris, France
 - Alexandra Dürr, MD PhD (AD)
- Universiteit Leiden, Netherlands
 - Raymund Roos, MD (RR)

Other sites in Europe and North America may be necessary depending on future power calculations and ongoing data analysis.

A schematic of the site selection process that was used to select sites is shown in Figure 3.

4.4 Steering committee

The Track-HD steering committee will be *ad hoc* and dynamic, but will contain key members representing each area of study.

- Members TBA

4.5 Other key investigators and expert advisors in Track-HD

Additional consultants and investigators will be utilized during the course of the Track-HD study.

Site selection

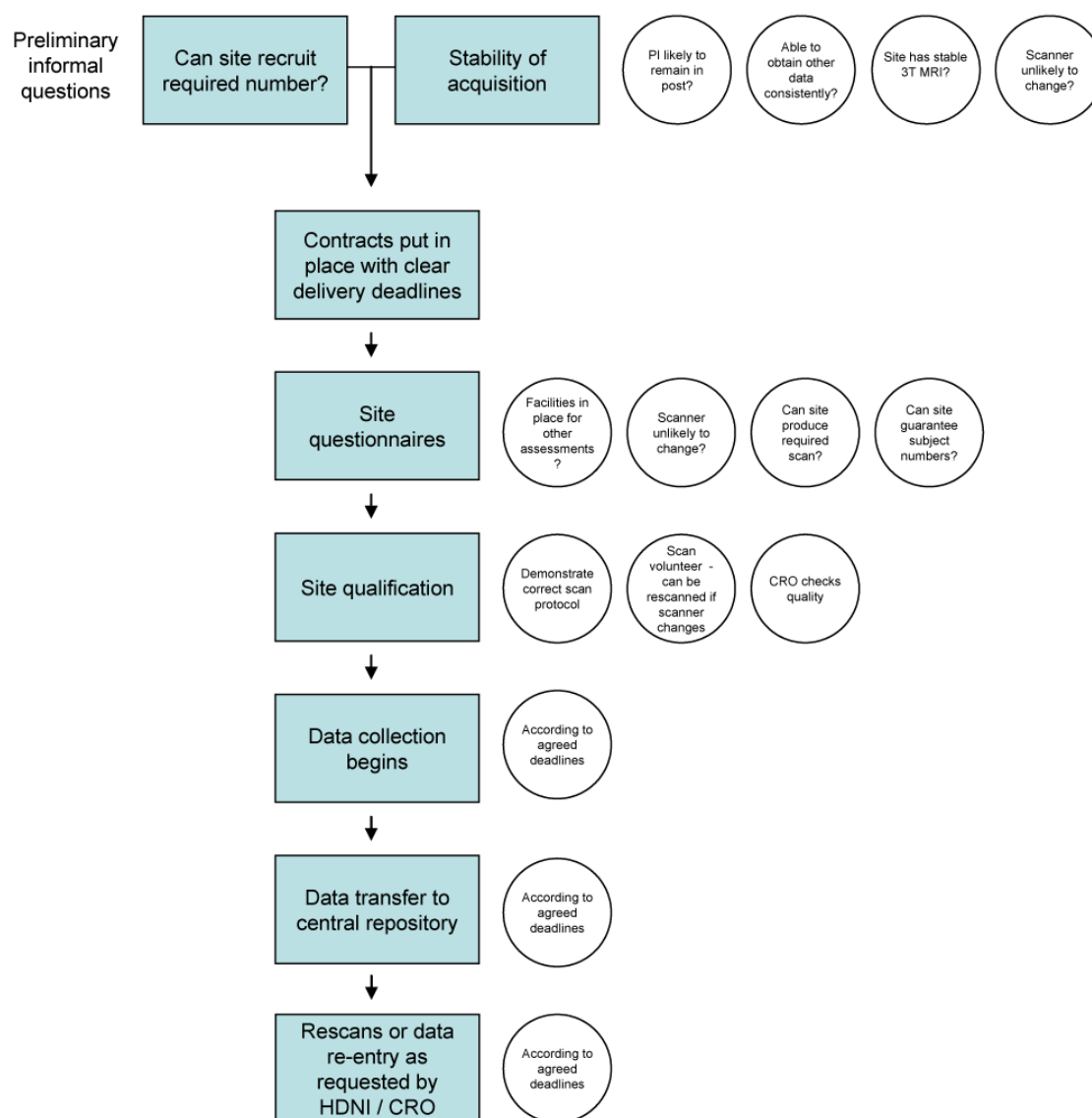


Figure 3 Study site selection schematic

4.6 Funding

Track-HD is funded by the High Q Foundation Inc, New York, NY USA.

4.7 Study period

Track-HD is a prospective study for which each patient is enrolled for 24 months. The study duration per centre is 36 months. The start date for all sites is January 2008. The projected end date including all data processing and analysis is December 2010.

4.8 Study objectives

The primary aim of the study is to provide essential methodological advances needed for optimizing neuroprotective clinical trials in premanifest and early HD. Specifically, Track-

HD will be used to examine the sensitivity of individual and combined clinical and biological outcome measures for tracking progression. The secondary aim is to determine what combination of measures is the most sensitive for detecting change over the natural course of premanifest and early HD, with a view to validating these as potential outcome measures for use in future therapeutic trials.

The goals of Track-HD and integration within the HD clinical assessment pipeline (Figure 1) are summarised in section 3.

4.9 Study population

Each centre will recruit 90 subjects drawn from the population of its HD clinical service. The typical cohort at each centre will be 30 control subjects, 30 premanifest HD expansion carriers and 30 subjects with early disease (stage 1 or 2).

Subjects with early disease are needed not only because such subjects are expected to be enrolled in disease-modifying trials, but also because they allow contextual evaluation of measures found to predict progression in the premanifest cohort. Without early manifest subjects, the significance of changes identified in the premanifest cohort in terms of the trajectory of the disease will not be known.

In order to increase the yield of disease-related changes in the premanifest cohort, a burden of pathology selection criterion will be used. Burden of pathology severity is given by $(\text{CAG} - 35.5) \times \text{age}$. A threshold of >250 CAG-years will be set, which approximates to 15 years to estimated onset (calculations based on Predict-HD dataset by Doug Langbehn).

Control subjects will be normal repeat length siblings not carrying the expansion mutation, non-family persons known not to carry the expansion mutation and partners or spouses of research participants. Such individuals share genetic, environmental, social and dietary exposures as well as some psychological burden of living with HD.

The decision to use partner/spouse controls and normal repeat length persons rather than untested at-risk individuals was reached after a careful consultation process and is based on the following rationale:

- Untested at-risk individuals may individually have certain characteristics (such as motivation) that make them good controls for certain neuropsychiatric tasks.
- However, using at-risk individuals effectively reduces by 50% the number of “true” gene-negative controls.
- At-risk subjects who tested positive would tend to be so far from onset that analyses using their data would be poorly powered.

It is important for reasons of patient retention, patient satisfaction, morale and for practice effects that the Track-HD premanifest cohort be distinct from the already enrolled participants in Predict-HD.

4.10 Study design

All subjects will be assessed at baseline, 1 year and 2 years. At each visit, subjects will undergo clinical, motor, cognitive, neuropsychiatric, MRI and oculomotor assessment as well as donating blood samples (See Table 2). Each visit will last approximately 7 hours.



General	<ul style="list-style-type: none"> • Informed Consent/In-Exclusion • History (medical, disease, psychiatric) • Invariable Demographic Data • Co-morbid Conditions • Concomitant Medication • Family History • CAG • Variable Demographic Data
Clinical History and Ratings	<ul style="list-style-type: none"> • UHDRS '99 TFC • SF 36 • Quality of Life Index • UHDRS '99 Motor • Functional
Neuropsychiatric Assessment	<ul style="list-style-type: none"> • Short Behavioural Assessment - PBA • Becks Depression Inventory Version II - BDI II • Hospital Anxiety/Depression Scale - HADS • Snaith Irritability Scale - SIS • Frontal Systems Behaviour Inventory - FrSBe (Pat) • Irritability Scale for Huntington's Disease - ISHD (7 days)
Biosample Collection	<ul style="list-style-type: none"> • Samples (DNA and LB lines at Baseline) • ADC tube for DNA & lymphoblastoid cell line
Cognitive Assessments	<ul style="list-style-type: none"> • Core Cognitive Battery <ul style="list-style-type: none"> ◦ <i>Trails A - B</i> ◦ <i>Smell Identification Test</i> ◦ <i>Static Negative Emotion Recognition</i> ◦ <i>Symbol Digit Modalities Test</i> ◦ <i>Stroop Word Test</i> ◦ <i>Speeded Tapping</i> ◦ <i>Self-Paced Tapping, 550 Pace</i> ◦ <i>IQ Covariate</i> • Experimental Battery of Promising Tests <ul style="list-style-type: none"> ◦ <i>Speeded Tapping with Cognitive Load</i> ◦ <i>Self-Paced Tapping Alternate Pace</i> ◦ <i>Mindstreams Visual Spatial Imagery Task</i> ◦ <i>Circle Tracing Task</i> ◦ <i>Visual Array Comparison Task</i>
Quantitative Motor Assessments	<ul style="list-style-type: none"> • Brainstem Motor Coordination Test • Upper Extremity Motor Coordination Test • Bradykinesia Test • Gait Test • Posturography for Lower Extremity Motor Coordination Test • Graphimetry
Imaging	<ul style="list-style-type: none"> • 2 back-to-back 3T MRI scans (T1) • 1 T2 Scan • 1.5T scans (2x) at baseline and one year on subset of 25%
Oculomotor Assessments	<ul style="list-style-type: none"> • Second Order Conditional Conflict Task • Baseline Saccade Latency and Velocity

Table 2 Study assessments

4.11 Quality control and quality assurance

Stringent local and central QC/QA measures will be in place. All personnel will be trained and assessed for inter-rater reliability before beginning patient assessments and on an ongoing basis with annual retests. Imaging QC will ultimately be centralised under the control of HDNI which will employ an imaging CRO for the purpose of site specification and QC/QA. All measures will be automated or computer-administered to the maximum possible extent and all rater-dependent measures (UHDRS and SBA) will be video recorded for central QC by expert raters.

4.12 Data storage and security

Phenotypic and imaging data will be pseudonymised and securely stored by CTMS, Ulm and LONI, Los Angeles, respectively. Pseudonymised biosamples will be stored by the biorepository at Biorep, Milan. All agencies responsible for data storage will observe the highest precautions to ensure data integrity and security.

4.13 Data flow

Data and biosamples will be stored, checked and monitored centrally by appointed data repositories and monitors. The pathways for data collection, storage, checking and analysis are outlined below (Figure 4).

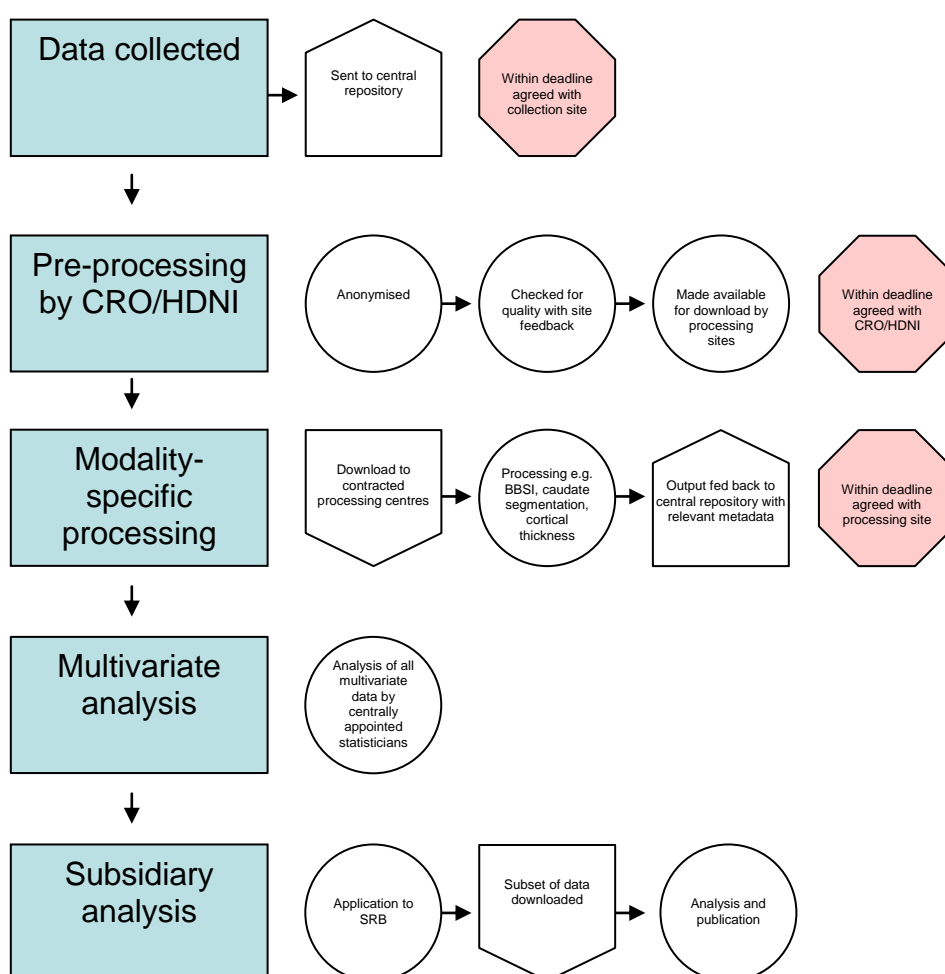


Figure 4 Data flow schematic

After minimal essential **local QA** (e.g. entering Subject ID into the oculomotor data), all data will be transmitted to a central server.

Central QA will be conducted by nominated agencies (e.g. Imaging CRO for imaging data). “Clean” data will then be stored in the distributed central data repository (i.e. LONI/HDNI for imaging at UCLA in Los Angeles, CTMS for clinical data at EHDN in Ulm, CRB for biological samples at Biorep in Milan) and distributed to study centres for en masse **modality-specific processing** – e.g. caudate segmentation, cortical thickness measurements, CAG sizing, etc. See Section 5.15.

The **key question** of the study — what combination of measures best captures disease progression over one year — should be centrally managed by the Steering committee with our biostatisticians. Clinical Neurology fellows and Psychologists at the 4 study sites may be involved in data analysis in the interim period between assessments.

4.14 Organisation

The Principal Investigator is Dr Sarah Tabrizi, London. She will head a Central Coordination Team consisting of a full-time Clinical Trial Manager, Project Manager and Study Administrator. The Central Coordination Team will be responsible for finalising the study protocol and liaising with sites and other agencies (data repositories, data monitors, expert advisors) to ensure that the study is ready to begin at all sites by January 2008. The Team will be guided by High Q and the Steering committee (Figure 5).

Track-HD Organisation –

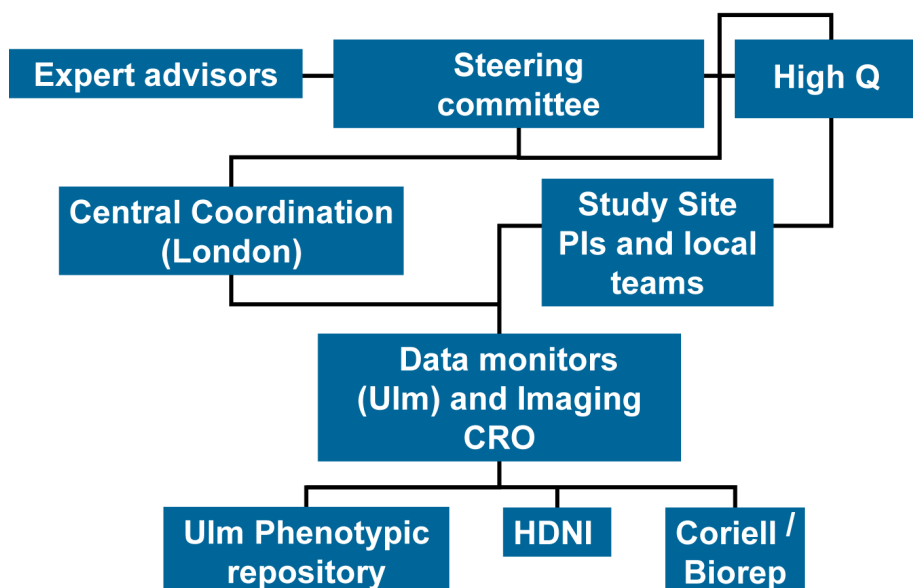


Figure 5 Track-HD organisation

4.15 Study management

Besides the Imaging CRO, Track-HD will not involve a CRO. Instead, the roles that might be occupied by a CRO will be devolved to other organisations already involved in the study, as detailed below (Table 3).

Role	Responsibility
Project management and planning	<ul style="list-style-type: none"> Study coordination team Steering committee High Q
Regulatory documents (IRB)	<ul style="list-style-type: none"> Study coordination team
Conducting investigator meetings	<ul style="list-style-type: none"> Study coordination team
Conducting study expert meetings	<ul style="list-style-type: none"> Study coordination team
Training of personnel	<ul style="list-style-type: none"> Centrally coordinated (EHDN/Julie Stout) motor and cognitive rater assessments
Site identification and selection	<ul style="list-style-type: none"> High Q Study coordination team
Initiation visits	<ul style="list-style-type: none"> Study coordination team
Monitoring visits	<ul style="list-style-type: none"> Study monitoring team at EHDN, Ulm Direct on-line data monitoring
Management of laboratory samples	<ul style="list-style-type: none"> Biorep
Quality assurance	<ul style="list-style-type: none"> HDNI (with imaging CRO) EHDN Biorep Cognitive (Julie Stout and colleagues)

Table 3 Study management roles and responsibilities

HDNI will contract an imaging CRO to establish and coordinate aspects of the imaging infrastructure, namely:

- Study set-up
- Site qualification
- Protocol definition
- Training
- Data anonymisation and transfer
- Clinical read of baseline scans
- Assessment of scan quality and consistency
- Site communication and troubleshooting

5 Detailed study description

5.1 Background

Huntington's disease (HD) is an autosomal dominantly inherited, progressive neurodegenerative disorder characterized clinically by a movement disorder (typically chorea), neuropsychiatric disturbances, and cognitive impairment. The clinical features of HD usually emerge in adulthood (mean age of 37 years), after which illness progresses steadily over a period of 15-25 years. Genetic testing (preceded by genetic counselling according to internationally accepted guidelines) allows one to determine whether a clinically normal person harbours the HD mutation and thus predict that a person will go on to develop HD before he or she shows clinical symptoms and signs. HD has a prevalence of 5-10 per 100,000 in the general population of the Western hemisphere. HD affects at least 40,000 people living in Europe. In addition, an estimated 80,000 individuals carry the HD mutation but remain as yet unaffected. HD is caused by an expansion of a cytosine-adenine-guanine (CAG) trinucleotide repeat stretch in exon 1 of the HD gene on chromosome 4. Individuals who have 36 CAG repeats or more may develop the clinical symptoms and signs of HD including motor, cognitive and neuropsychiatric abnormalities that cause a progressive loss of functional capacity and shorten life. The course of HD is relentless; to date, there is no treatment which has been shown to alter the progression of the disease (Bates, Harper, & Jones, 2002).

Since the gene mutation responsible for HD was identified in 1993, considerable 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 (Handley et al., 2006). Systematic screening efforts to identify compounds with disease-modifying properties are under way, and some compounds have been reported to result in beneficial effects when applied in model systems of HD (Ona et al., 1999; Hockly et al., 2003) thus providing a rationale for identifying well-tolerated and clinically effective novel treatments for HD. However, currently the predictive value of these promising results obtained in model systems for HD patients is unknown. Despite these advances, a more seamless integration of basic, translational and clinical HD research is required to plan and conduct future clinical studies, e.g. by identifying and validating biological markers that track the course of HD ('state biomarkers'), and by identifying factors that influence the onset and progression of illness.

5.2 Rationale

Early, sensitive measures of disease progression will support the scientific and economic feasibility of future therapeutic trials, particularly in the premanifest population. In cross-sectional studies premanifest HD patients show a number of significant differences from non-expansion carriers as long as 10 years before diagnosis. Apparent early changes have been found using (1) cognitive assessments (Paulsen et al., 2006), (2) caudate and putamen volumetry (Aylward et al., 2004), (3) whole-brain atrophy measurement (Henley et al., 2006), (4) cortical thickness measurement (Rosas et al., 2005), (5) voxel-based morphometry (Kassubek et al., 2004), (6) laboratory biomarkers (Hersch et al., 2006) (Borovecki et al., 2005) (Borrell-Pages et al., 2006), and (7) raclopride (D2 dopamine receptor) binding (Pavese, et al., 2003), and (8) oculomotor assessment. (Golding et al., 2006). At least some of these differences have been followed longitudinally in a limited number of subjects, but no coordinated studies are presently available with sufficient power to compare the sensitivity of these different measures. Thus, although a number of measures are known to track change at various stages of the disease, as yet little is known about associations between measures and their combined predictive value. It is also particularly important to investigate changes over short intervals in order to try and minimise the time needed for subsequent therapeutic trials to show an effect.

Track-HD is an international, multi-centre study which is designed to determine the individual and joint utility of a selected set of clinical and biological outcome measures. Track-HD integrates prospectively- and systematically-collected clinical research data (e.g. phenotypic clinical features, family history, demographic characteristics) with biological specimens obtained from individuals with manifest HD, unaffected individuals known to carry the HD mutation, and controls. We will measure clinical and biological markers, including



neuropsychiatric, cognitive, quantitative motor, oculomotor, imaging markers, and laboratory biomarkers.

Track-HD will complement other High-Q funded prospective studies, Registry and COHORT, as well as NIH-sponsored prospective studies, Predict-HD (prospectively examining phenotypes among unaffected subjects who following predictive testing are known to carry the HD mutation), and PHAROS (examining phenotypes among unaffected subjects with an affected parent who have unknown expansion carrier status, having chosen not to undergo DNA testing) by adding to the clinical and biological markers that are being studied.

Since its initial description in 1872, it has been clear that HD has a strong hereditary contribution resulting in the generational transmission of the disease from parent to offspring, regardless of gender (Bates, Harper, & Jones, 2002). Beginning in 1981 and through the collection of clinical and family history information and biological material (DNA) from HD families the gene and the mutation causing HD was identified in 1993 (The Huntington's Disease Collaborative Research Group, 1993). 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. There is a strong and consistent inverse relationship between the length of the CAG repeat and the age at clinical onset of HD (The Huntington's Disease Collaborative Research Group, 1993; Langbehn et al., 2004; Penney et al., 1997). However, the size of the CAG repeat accounts for only about 60-70% of the variance in age at onset; other, as yet unidentified factors influence age at onset and the cascade of pathogenic events resulting in the HD phenotype. Recent studies suggest that the remaining variation in age at onset of HD is strongly heritable (Wexler et al., 2004). These findings indicate that the onset of HD is substantially influenced by factors other than repeat size, and that other modifier genes may determine the remaining variation in age at onset.

Owing to the limited availability of prospectively collected, longitudinal data of sufficient quality, studies to identify genetic modifiers of the rate of disease progression or the pace and extent of abnormalities seen on neuroimaging have not been performed to date. Identification of genes that modify the pathogenic process in HD offers a direct route to validate targets for development of HD experimental therapeutics. Track-HD will provide a wide range of HD-associated phenotypes by which to identify modifier genes. Initially, the phenotypes available will be derived from clinical assessments (UHDRS), but the collection of biological samples will also permit the study of additional phenotypes at the levels of RNA, protein, metabolites and cultured cells. The combination of phenotypic and genotypic information will permit analysis of relationships between individual polymorphisms and genes and the effect they have on modifying the phenotypic presentation, rate of progression and response to treatment of HD using genetic linkage and genome-wide association strategies.

The clinical database on HD and the biomaterials to be collected for the Track-HD study will be used for a variety of analyses which may be broadly categorized as either cross-sectional or longitudinal. The sample size was selected to ensure sufficient statistical power for determining the sensitivity of selected assessment tools for monitor the progression of HD and for detecting molecular determinants or markers for clinically relevant phenotypic characteristics or outcomes (e.g. progression of HD and a better definition of the clinical onset of disease). This will, in turn, improve the efficiency of therapeutic trials by providing more and more clearly defined endpoints (e.g. delaying onset of clinical disease).

5.3 Objectives

Track-HD is designed to relate phenotypic characteristics in as many modalities as can be measured (clinical, cognitive, quantitative motor, oculomotor, neuropsychiatric, imaging, laboratory) and genetic factors, in order to relate phenotypic characteristics, genetic factors ('genetic modifiers'), data derived from the study of blood ('wet biomarkers') and imaging data ('dry biomarkers').

It is possible that the cohort in this study will be recruited into the earliest multi-centre, biomarker-driven clinical trials of disease-modifying agents. As such, the data collected to date will form the observational arm of an observation-intervention study.

The primary objective of this study will therefore be to determine what combination of measures is the most sensitive for detecting change over the natural course of HD, with a view to validating these measures for use in future therapeutic trials.

There are two key features of Track-HD. First is flexibility of the study protocol. Many cross-sectional studies of potential clinical tests are in progress and those that look promising will be rapidly implemented into Track-HD. Therefore the protocol will be flexible and will likely change as new tests become available.

In addition, the selection of outcome measures is based on an evidence-based framework as described below.

5.4 Study design

Track-HD will be a 3-year natural history study (2-year involvement for each subject) of premanifest and early HD (Shoulson and Fahn stage 1 and 2) (Shoulson & Fahn, 1979; Shoulson, 1981). Each centre will recruit 90 subjects: 30 control subjects, 30 premanifest individuals and 30 early disease subjects. All subjects will be assessed at baseline, 1 year and 2 years. Subjects will undergo clinical, neuropsychiatric, cognitive, quantitative motor, oculomotor and MRI assessment as well as donating blood samples at baseline, one year and two years. Shorter time interval assessments may be instituted following the one-year data analysis if there is evidence for robust change over one year in any assessment. Updates to the assessment protocol will occur annually or sooner if needed so that new methods and findings can be dynamically incorporated to enhance the design and usefulness of the study.

Clinical phenotypic data will be assessed and documented based on information obtained from three sources:

- Trained assessors who record their clinical impression using rating scales (i.e. UHDRS motor);
- Subjects themselves who report on their subjective experience (i.e. Hospital Anxiety and Depression Scale, Snaith Irritability Scale, and Beck Depression Inventory-II);
- Partners who report on the level of function and neuropsychiatric aspects of the subject.

For a given subject, the same investigator should carry out the assessment throughout the study where possible.

5.5 Track-HD study assessments

5.5.1 Evidence-based framework for assessment planning

Evidence-based assessment (EBA) refers to the application of uniform standards of evidence to evaluate chosen measures and/or to optimize the selection of measures to address clinical questions. Measurement is a ubiquitous feature of research; however, often measurement strategies are developed without explicit consideration of the strength of evidence for the use of particular measurements. For the Track-HD study, we propose to apply a system of evidence-based assessment that uses the quality, quantity, and consistency of evidence about test sensitivity in premanifest and early HD to inform test selection, and, where test selection has been driven primarily by expert input, to evaluate the limits of existing evidence for sensitivity of expert-selected tests.

Rationale for Using EBA

The rationale for using the EBA approach is to improve the potential value of the measurements taken in Track-HD in the following ways:

1. Where adequate evidence exists, such as for some aspects of cognitive assessment in premanifest and early HD, EBA guides evaluation of the existing evidence to inform the selection of measures that have the greatest levels of sensitivity along with the strongest evidence for that sensitivity.
2. In cases where sufficient evidence does not exist, applying the EBA framework highlights what evidence is needed, and allows a selected test's value (for example a test proposed by an expert but for which longitudinal evidence in premanifest and/or early HD is lacking) to be considered in the context of what is and is not known about its potential usefulness.
3. Data from tests which have strong evidence can also be used to set benchmarks that new tests must meet or surpass to be considered useful contributors to the measurement strategy for the study. (Note that redundancy between tests is also a consideration here).
4. Finally, because the EBA approach applies the same metrics across all types of measurements, it also facilitates a comparison across domains, such as quantified motor, cognitive, neuropsychiatric, imaging, and wet biomarkers to allow the relative contributions of various types of measures to be considered in the broader context of their possible contributions to sensitivity of measurement of the entire study.

Figure 6 below provides a conceptual framework for the integration of empirical evidence, expert input, and pragmatic considerations being used in the development of assessment strategies for Track-HD and ultimately clinical trials.

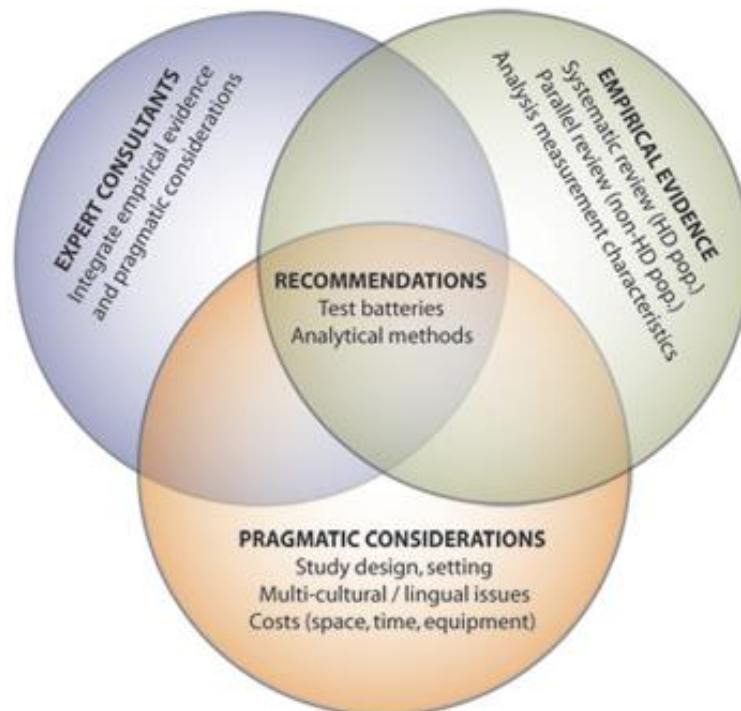


Figure 6 Framework for evidence-based assessment

- 1) The empirical evidence circle includes:
 - a) systematic review of existing empirical evidence that is most closely related to the research question;
 - b) further systematic searches in response to expert suggestions, on measurement domains/techniques not well-represented in the existing published literature, and novel instruments that do not yet have sufficient presence in the literature to be evaluated in the systematic review; and,
 - c) metric analyses of variables that are obtained from instruments, including distributional properties of the data, suitability of the level of difficulty, reliability.
- 2) The expert input circle includes information derived from local experts and all consultants regarding what constructs should be assessed, what is missing from the currently available empirical evidence, what measurement methods are most appropriate to the research question, and what potential data analytic strategies might be useful.
- 3) The pragmatics circle includes information about the measures being considered that might weigh on the suitability of particular instruments for this study and ultimately future clinical trials. The setting of the study (number of sites, availability of space for equipment and personnel, whether testing will take place in multiple languages), and the expertise types and levels of the personnel available to collect the data. Regarding the measures being considered, pragmatics includes the dollar costs for materials and instruments, the availability of materials and instruments, the time requirements for the assessment and scoring, the expertise requirements of the person who will administer the measure, and the amount and characteristics of the space needed to perform the measurements.

The intersection of these three circles symbolizes the need for integration of information from all three circles for final recommendations on measures to be made. Note that for Track-HD, whereas some measures will be selected for their known sensitivity to the disease process during premanifest and early HD, a key feature of that protocol is that a small number of “promising” measures are also selected to further expand and refine our measurement options for future studies.

5.5.2 Demographic information

Patient group (Control / PM / HD); invariable demographical data (Date of birth; Sex; Ethnicity; Handedness; Education level; Education years) and variable demographic data (Height (cm); Weight (kg); Occupation; Occupation category; Employment (full-time; part time; unemployed; retired); Marital status).

5.5.3 Clinical assessment

The steady worsening of the motor, cognitive, and neuropsychiatric capacities of HD patients results in progressive functional decline. Clinical rating scales aimed at capturing the clinical phenotype and mirroring the progression of the illness have been widely used to establish the rate of functional decline in a variety of HD populations. The Unified Huntington's Disease Rating Scale (UHDRS) was developed by the Huntington Study Group (HSG) in 1993 and revised in 1999 as UHDRS 99 (The Huntington Study Group, 1996; Marder et al., 2000). The UHDRS 99 assesses four major clinical domains of impairment: (1) motor, (2) cognitive, (3) neuropsychiatric, and (4) functional capacity. In devising this scale, items were selected that were likely to be sensitive to measure progression in early stages of the illness. The UHDRS 99, of which the motor and functional domains will be employed in Track-HD, has been used in all clinical sites collaborating as HSG in North America, Europe, and Australia. The UHDRS has undergone extensive testing of reliability and internal consistency (The

Huntington Study Group, 1996; Marder et al., 2000) and has been shown to have a good inter-rater reliability for the total motor score. The motor section of the UHDRS correlates strongly and significantly with the functional component of the UHDRS. Internal consistency, as measured by Cronbach's alpha, was 0.95 for the motor component and 0.95 for the functional component of the UHDRS (Shoulson & Fahn, 1979). The UHDRS has been used widely in HD clinical trials. (Hersch et al., 2006; Tabrizi et al., 2005).

Motor assessment: The UHDRS motor examination will be administered; this is the gold standard for HD.

Past medical history: Birth trauma or neonatal illness; Birth / neonatal illness details; Childhood illness <12; Illness <12 details; Illness 13-17; Illness 13-17 details; Surgery; Surgery details; Alcohol units per week; Alcohol status (never abused; previous abuse; current abuse); Recreational drug use; Tobacco (Current; ex; never); Cigarettes per day; Years of smoking; Allergies.

Medication: Name; dose; duration for each; Active medical conditions.

Huntington's disease history: Affected parent; Parental onset age; Onset age according to patient; Onset age according to family; Onset age according to rater; First symptom according to patient; First symptom according to family; First symptom according to rater (evaluation of clinical onset will be detailed and based on the EHDN "symptom age at onset" questionnaire (see Track-HD SOP documents); Date of genetic test; Analysing laboratory; Small allele length; Large allele length.

Psychiatric history: Previous depression; Previous anxiety disorder; Previous OCD diagnosis; Previous psychotic illness; Previous suicide attempt; Previous self-harm; Previous suicidal ideation.

5.5.4 Family History Questionnaire (FHQ)

A questionnaire will be handed to consenting participants to share their family tree by indicating their siblings, children and relatives up to the second degree and by volunteering the following information on each person within the family tree: gender, year of birth, alive/dead (for those deceased: year of death/age at death and – as best as participants can tell – cause of death), opinion whether in the view of the contributor a member of a family is affected with HD/carries the HD mutation, (for those affected with HD/carrying the HD mutation: age at time of HD diagnosis/predictive testing, first signs and symptoms and whether the diagnosis of HD was confirmed by physician/genetic testing). These data will be recorded first in a source data file document (see Source Data File Family History in Track-HD SOP documents). From these data a graphical representation of a family tree will be generated using appropriate software (see Track-HD SOP documents). In order to protect the confidentiality of the information contained within the family tree, annotations (affected by HD, mutation carrier, participant in Registry/Cohort) will be visible only on demand. Within this family tree the symbols representing those members of the family who consented to participate in Registry will be annotated with their pseudonyms; family members who did not consent to participate in Registry will be represented with symbols without an annotated pseudonym. By using this procedure, biosamples and clinical data of related participants (which is essential e.g. to identify genetic modifiers by sib pair analysis) can be linked while protecting the privacy of individuals volunteering information through the use of pseudonyms (participants in Registry/Cohort) or anonymous codes (not participating in Registry/Cohort), respectively.

The source data file for the FH component is provided in the Track-HD SOP documents.

5.5.5 Functional & Quality of Life (QoL) assessments

5.5.5.1 Overview of the functional and QoL battery

Time required: 7 minutes at study visit, 20 minutes at home before study visit-participant

Summary

The goal of the Track-HD functional/QoL battery (Table 4) is briefly to assess current functional abilities and participants' subjective report of their quality of life and to relate findings to progression of disease and to cognitive, motor/oculomotor, imaging, neuropsychiatric and wet biomarker measures in the Track-HD study. To achieve this goal, the functional/QoL assessment includes: Clinician-based assessment and self-report measures of function and quality of life. Thus, not only will the clinician point of view be considered, but also, we will document the participants' subjective experiences of functional abilities, well-being, and life satisfaction.

For participants:

1. a brief interview to assess current functional abilities, which will be administered by a trained rater as part of the study visit (UHDRS TFC)
2. the Short-Form 36 (SF-36), to be completed at the at home, before the study visit
3. the Quality of Life Index (QOLI), to be completed at home, before the study visit

List of Tests	Abbrev	Rating Type	Time (min)
UHDRS Total Functional Capacity	TFC	Clinician rated	5
Short Form 36	SF-36	Self rating	Home 10 /Clinic 1
Quality of Life Index	QOLI	Self rating	Home 10 /Clinic 1

Table 4 Functional & QoL assessments

Rationale for task selection

Whereas functional changes are well documented in middle to late stage HD (Marder et al., 2000), less known about this aspect of premanifest and early HD. Yet, subtle cognitive, psychiatric and motor changes may lead to altered productivity in the home, community and workplace. For example, a person with above average work performance may have to work more hours to maintain the same level of productivity. Alternatively, a person working at above average skill level may decline into an average level of performance, and therefore not be considered to have a significant impairment. In both of these cases, productivity changes would not be evident from simply looking at occupational status.

Thus, for a study of premanifest and early HD, it is essential to identify measures sensitive to the subtle functional changes that may occur prior to diagnosis with HD. One goal of the study is to better understand how changes in everyday functioning are related to cognitive, psychiatric, and motor function as well as neuropathology. A second goal is to contribute to efforts aimed at identifying functional and quality of

life measures that will be useful in future clinical trials. Some work on this topic is underway already in the Predict-HD study. Carissa Nehl, a Ph.D. student at University of Iowa, and her advisor, Jane Paulsen, have been studying a set of functional measures for use in pre-manifest HD, although results are not yet available. In addition, Aileen Ho and others from the Quality of Life Working Group of the EHDN are working on developing suitable measures for this task. In lieu of validated methods for sensitive evaluation of functional abilities and quality of life in pre-manifest and early HD, the Track-HD battery includes a short set of measures that will, it is hoped, contribute to these ongoing efforts. As data from these ongoing efforts becomes available, the Track-HD protocol may be modified to include alternate measures in this domain.

In this assessment category, the domains of greatest interest during premanifest and early HD are:

- Productive activities outside the home
- High order activities of daily living (e.g. finances, homemaking)
- Social functioning and adjustment
- Life satisfaction

The measures selected for the functional/QoL battery will provide a broad assessment of these four domains.

Scientific questions to be addressed by the Functional/QoL battery

Compared to the cognitive and motor domains, much less is known about how the course of functional decline in the transition from health to illness. For example, when, relative to onset, do specific functional and QoL changes begin, and what is the nature and rate of change across time? Do functional and QoL measures make a unique predictive contribution to measures of disease progression above and beyond that provided by other clinical outcome measures?

Additional considerations

An alternative method of quantifying functional status is the assessment of productivity in the workplace, home and community. There are a large number of self-report instruments used to assess health-related productivity (see Prasad et al., 2004 for review). As of yet, little data using productivity measures has been collected in premanifest or early HD, and at this time, the Track-HD study will not include a self-report productivity instrument as part of the functional/QoL battery. Hopefully initial results from the Predict-HD add-on study which is using the Endicott Work Productivity Scale will inform future assessments in Track-HD.

5.5.5.2 Information on specific instruments

UHDRS TFC

The goal of the UHDRS TFC is to obtain a clinician's assessment of the participant's *capacity* to perform in each of five functional domains including occupation, finances, domestic chores, activities of daily living, and care level. The TFC is a clinician rated 14-unit scale (range 0-13) with higher scores indicating higher function.

Rationale and strength of evidence for the selection of the UHDRS TFC

The UHDRS Total Functional Capacity Scale (TFC) was selected because it is sensitive in manifest HD and is a standard in the field for diagnosed HD. Thus, it will allow comparison of Track-HD findings with those of other studies. One limitation of the TFC is a lack of sensitivity at the upper end of the functional spectrum, likely to occur in premanifest HD. For example, subtle productivity changes in work

performance over time, would lead to only a one point change in TFC score. The other functional measures of the UHDRS, the Functional Checklist and the Independence Scale, have a relatively greater focus on more basic activities of daily living (i.e., toileting, ambulation) compared to the TFC and thus, are less relevant to the target sample of Track-HD. The Functional Checklist and Independence Scale will not be included in Track-HD.

Short Form-36 (SF-36)

The goal of the SF-36 is to obtain self-ratings of physical and emotional health. The SF-36 is a 31-item self-report questionnaire which is commercially available, very widely used, and available in English, French and Dutch. Participants are asked to rate the frequency or severity of functional changes. Some items pertain to overall health and others specifically to physical or emotional health. There are two composite measures, Physical Health and Mental Health, and eight subscales (outlined in Table 5).

Physical Health Summary	Mental Health Summary
physical functioning	social functioning
role functioning secondary to physical limitations	social role functioning secondary to emotional issues
bodily pain	vitality
general health	mental health

Table 5 Composite measures of SF-36

Rationale and strength of evidence for the selection of the SF-36

The SF-36 was selected because it is a widely used measure of function, with solid psychometric properties. It has been shown to be superior to other measures in this domain. While there is no published data on the SF-36 in premanifest HD, Helder et al., (2001) found the physical functioning subscale to have a large effect size (-0.92 , $p=0.000$) in a mixed group of HD subjects (disease duration ranging from 1 to 25 years). Ho and colleagues (2004) compared the SF-36 to the Sickness Impact Profile (another self-report measure of function) in a group of HD patients with a wide range of severity. In mid to late stage HD, the physical functioning subscale showed the greatest correlational ES with disease duration ($ES=0.82$, $p=0.000$) < 1 . These authors reported that the SF-36 had better construct validity and test-retest reliability than the Sickness Impact Profile. Moreover, unlike the Sickness Impact Profile, motor symptoms did not appear to influence the non-motor sections of the SF-36. In addition, the SF-36 required less time to administer.

Quality of Life Index (QOLI)

The goal of the QOLI is to obtain self-report of overall life satisfaction, as well as ratings of specific aspects of quality of life including health/daily functioning, social/economic, psychology/spiritual, and family life. The QOLI, developed for use in clinical populations, is a 32-item self-report questionnaire which is commercially available. Participants are asked to rate each item 3-point rating scale for importance and a 6-point rating scale for satisfaction. Scores on individual items are summed to obtain an overall score and several subscales, with higher total scores indicating better quality of life. The QOLI is available in English and French, but translation into Dutch will be required.

Rationale and strength of evidence for the selection of the QOLI

The QOLI was selected because it has high internal consistency, test-retest reliability and validity in a variety of clinical populations (Ferrans & Powers, 1992). The QOLI is also being used in the Predict-HD sub-study on functional ability (led by Carissa Nehl and Jane Paulsen), and therefore, inclusion of this measure in Track-HD will provide a link between the two studies.

5.5.6 Neuropsychiatric assessment

5.5.6.1 Overview of the neuropsychiatric battery

Time required: 30 minutes at study visit-participant, 25 minutes at home before study visit-participant, 33 minutes at home before study visit-companion (when available)

Summary

The goal of the Track-HD neuropsychiatric battery (Table 6) is briefly to assess neuropsychiatric symptoms and relate findings to progression of disease and to cognitive, motor/oculomotor, functional/quality of life, imaging, and wet biomarker measures in the Track-HD study. To achieve this goal, the neuropsychiatric assessment includes:

For participants:

1. a brief interview to survey neuropsychiatric signs and symptoms associated with HD (PBA Short Form), which will be administered by a trained rater as part of the study visit
2. the BDI-II, to be completed at the study visit
3. the HADS/Snaith Scales for depression, anxiety, and irritability, to be completed at home, before the study visit
4. the FrSBe, to be completed at home before the study visit

For companions, if available:

1. a companion version of the HADS/Snaith Scales
2. a companion version of the FrSBe
3. irritability ratings for seven days using the diary-based DAIR form

List of Tests	Abbrev	Rating Type	Time (min)
EHDN Behavioural Assessment – Short Version	PBA-S	Clinician rated	22
Beck Depression Inventory – Version II	BDI-II	Self-rating	6
Hospital Anxiety and Depression Scale	HADS	Self rating	Home (5)
Snaith Irritability Scale	SIS-self	Self rating	Home (4)
Snaith Irritability Scale	SIS-other	Companion rating	Home (4)
Frontal Systems Behaviour Inventory-Self Rating Test Booklet	FrSBe-self	Self rating	Home (15)
Frontal Systems Behaviour Inventory-Family Rating Test Booklet	FrSBe-other	Companion rating	Home (15)
Irritability Scale for Huntington's disease (SHD)	ISHD	Companion ratings	Home (2 min. x 7 days)

Table 6 Neuropsychiatric assessments

Rationale for test selection

The evidence base for selecting neuropsychiatric assessment tools is limited. Therefore, the design of this battery uses existing evidence from previous studies whenever possible, but relies strongly on expert input for selection of the majority of the tests. Self-rating scales have the great advantage that one can measure subjective mental events which are not apparent in outward behaviour. However, Chatterjee et al., (2005) compared patient and companion ratings of irritability in early HD and found only fair agreement. Surprisingly, patients with the most intact cognition had the lowest levels of agreement in irritability ratings with companions. Therefore, we will get both self and companion ratings for two of the ratings scales, the SIS and the FrSBe.

Scientific questions to be addressed by the neuropsychiatric battery. Compared to the cognitive and motor domains, much less is known about how neuropsychiatric signs and symptoms manifest and change in the course of progression from health to illness in HD. For example, when, relative to onset, do specific neuropsychiatric changes begin, and what is the nature and rate of change of these symptoms across time? What role do neuropsychiatric measures have in potential clinical trials of premanifest and early HD? What is the unique predictive contribution of neuropsychiatric signs and symptoms above and beyond that provided by cognitive and motor domains?

Additional considerations

An important consideration in designing the neuropsychiatric assessment for Track-HD is the recognition that depression and apathy can influence performance on cognitive and motor measures. Therefore, depression symptom severity and other neuropsychiatric variables are needed as covariates for analysis of cognitive and motor data. Neuropsychiatric measures may also be important outcome variables for tracking disease progression or effects of therapeutic interventions, although they may have limited sensitivity because they can be multiply influenced both by natural fluctuations as well as disease progression, and thus they may lack sufficient precision to sensitively reveal disease progression.

5.5.6.2 Information on specific instruments

EHDN Behavioural Assessment - Short version (PBA-S)

The goal of the PBA is to assess the following ten symptoms: low mood (i.e. depression), suicidal ideation, anxiety, irritability, angry outbursts / aggressive behaviour, lack of motivation (apathy), perseveration, paranoid thinking / delusions, hallucinations and behaviour suggesting disorientation. The PBA-S is a semi-structured interview that will be administered by study staff that has been trained to criterion for standardized PBA-S interview guidelines. Each item is rated for severity and frequency on a scale from 0 (absent and never, respectively) to 4 (severe and always, respectively). Severity and frequency scores are multiplied to achieve a score ranging from 0 to 16 for each item. Data analyses for Track-HD will include individual item and global (summed) scores. On average (in 9 videotaped participants with HD interviewed by Dr. Craufurd), the PBA-S required an average of 22 minutes (range 17 – 31 minutes) for administration.

Rationale and strength of evidence for the selection of the PBA-S

Selection of the PBA short form for Track-HD was on the basis of expert input from Dr. David Craufurd, who is psychiatrist and a widely recognized expert on the psychiatry of HD. The PBA is very similar to the UHDRS psychiatric assessment, but has been revised by David Craufurd and the EHDN Behavioural Phenotype Working Group to improve administration and scoring guidelines as well as, hopefully, reliability of this instrument. The PBA is a shortened version of the earlier

Problem Behaviours Assessment for HD (Craufurd et al., 2001). Although the PBA in its original form is effective in assessing neuropsychiatric symptoms in HD (Thompson et al., 2002), little data is available as yet on the PBA short form. Therefore, its sensitivity in premanifest and early HD is not known, and no effect sizes have been estimated. Similarly, reliability and validity have not yet been characterized. Dr. Craufurd plans to examine these psychometric characteristics of the PBA by collecting a series of more than 100 videotaped interviews in several languages and obtaining primary and secondary ratings for examination of interrater reliability.

Beck Depression Inventory II (BDI)

The goal of the BDI-II is to obtain self-ratings of the mood, somatic, and cognitive symptoms of depression. The BDI II is a 21-item self report questionnaire which is commercially available and very widely used. Participants are asked to rate each item on a 4-point scale (0, 1, 2, 3) reflecting severity of a symptom. Scores on individual items are summed to determine depression severity, with higher total scores indicating more severe depressive symptoms.

Rationale and strength of evidence for the selection of the BDI-II

The BDI was selected on the basis of existing evidence for its sensitivity in premanifest and early HD. The BDI has been widely used in cross-sectional studies of HD. Using meta-analysis, ESs (Cohen's *d*) (Cohen, 1988) for premanifest and early HD are - 0.46 ($p=0.002$) and - 0.82 ($p=0.006$), respectively, which are medium to large effects. The Predict-HD study is collecting longitudinal data on the BDI-II which will eventually be useful in estimating the longitudinal sensitivity of the BDI-II however these results are not yet available. A potential limitation of the BDI-II for assessing depression in premanifest and early HD is that somatic items relating to, for example, fatigue and appetite, may be confounded by HD, and therefore the total score may not accurately reflect severity of depression in the Track-HD sample. To address this problem, BDI-II scores can be recomputed without these items, and as well, item and factor analyses may be undertaken to determine the most sensitive items and the inter-item relationships.

Hospital Anxiety/Depression Scale (HADS)

The goal of the HADS is to obtain a brief rating of depression and anxiety symptoms that reflects primarily mood rather than cognitive and somatic symptoms. This commercially available scale has 14 items, 7 measuring anxiety and 7 measuring depression producing separate anxiety and depression sub-scores. Each item is rated on a four-point scale. Individual item and global (summed) depression and anxiety sub-scores will be analyzed. In addition, the HADS and the BDI will be compared for their sensitivity in this population and therefore will be useful in informing future studies.

Rationale and strength of evidence for the selection of the HADS

The HADS was selected on the basis of expert input from David Craufurd. He cites an advantage of the HADS over the BDI-II in that the HADS is less susceptible to confounds from the somatic symptoms in HD. At this stage, there is no evidence available in premanifest or early HD, although the scale is reportedly being used in a validation study (against the SCAN – Schedule for Clinical Assessment in Neuropsychiatry) by Jenny Keylock from Hugh Rickard's group at the Queen Elizabeth Psychiatric Hospital in Birmingham.

Snaith Irritability Scale (SIS)

The goal of the SIS is to obtain brief ratings of irritability by self and companion (two separate forms). The scale is composed of 8 items each rated on a four-point

scale. Four items are focused on inwardly focused irritability and four items are focused on outward irritability. Individual item and global (summed) inward and outward irritability sub-scores will be analyzed as well as a total scale score. Cross-validation with PBA and DAIR indexes of irritability will also be performed.

Rationale and strength of evidence for the selection of the SIS

The SIS was selected because it is the only measure of irritability we could identify that has been shown, in self-ratings only, to be sensitive to changes in premanifest HD. According to the report by Berrios et al. (2002), compared to controls, premanifest HD subjects rated themselves as more irritable than control subjects (both inward and outward irritability (Cohen's d ES= 0.67, $p=0.002$, medium). In addition, both subscales were correlated with estimated time to onset in premanifest HD (inward irritability ES=0.62 and outward irritability ES=0.89; (Berrios et al., 2001)). We found no longitudinal reports or companion rating studies using the SIS in HD.

Frontal Systems Behaviour Inventory (FrSBe)

The goal of the FrSBe is a 46-item behaviour rating scale that is intended to measure behaviour associated with damage to the frontal systems of the brain. Separate rating forms are available for the participant (Self-rating Test Booklet) and the companion (Family Rating Test Booklet. Each FrSBe form yields a Total score and scores for subscales measuring Apathy (14 items), Disinhibition (15 items), and Executive Dysfunction (17 items). Each item is rated on a 5-point Likert scale.

The FrSBe has been used in the Predict HD study and preliminary analyses demonstrate some sensitivity in premanifest HD. In addition, comparison of companion and subject ratings has yielded some specific discrepancies which will be further analysed in the Track study. Hamilton et al. (2003) showed that this rating scale was sensitive to changes occurring between the premanifest period and early HD.

Irritability Scale for Huntington's Disease (ISHD)

The goal of the ISHD is for companions to provide a diary-type assessment of irritable and aggressive behaviour over the course of one week. The spouse (or another household member) is asked to complete a simple form (by checking boxes) once daily for seven days, to rate severity and frequency of irritability, verbal aggression and physical aggression observed in the subject during the course of that day. Severity scores are multiplied by frequency scores to yield daily scores ranging between 0 and 16 for irritability, verbal and physical aggression, together with an overall total daily score between 0 and 48 arrived at by summing the 3 individual symptom scores. The daily scores can be summed to produce an overall weekly score between 0 and 112 for each of the three symptoms, together with a weekly total summary score ranging from 0 to 336.

Rationale and strength of evidence for the selection of the ISHD

The ISHD was selected on the basis of expert input from David Craufurd on the basis that irritability and aggression are two very important symptoms of HD that are perhaps poorly assessed by single time-point ratings. Also participants may be unaware of these behaviours. In a validation pilot study, David Craufurd (personal communication) collected data from 28 patients using the ISHD and the State-Trait Anger Expression Inventory (STAXI-II) (Spielberger, 1988, 1996) and found that spouse ratings were strongly correlated with the corresponding physician ratings for the same symptom using the PBA. In addition, while the patient STAXI correlations with both physician and spouse ratings are very good for about two thirds of the patients, they are quite discrepant for the remaining third. Evidence for sensitivity in premanifest or early HD is not yet available.

5.5.7 Biosample collection

All subjects will be invited to donate up to 50ml of blood for biomarker analysis at every visit. These will be collected by the site neurologist from all participants willing to donate blood. Biological specimens are donated with the understanding that all specimens are used for HD-related research, and that they are stored at a central biorepository. Samples will be processed on-site without delay to extract good quality plasma and divide it into 500µL aliquots for freezing. All consumables will be provided by Biorep on a per-patient basis and samples will be shipped to Biorep on a monthly basis. The sample for DNA and LB lines will be shipped at baseline on the day of collection. Plasma samples and PAXgene samples will be collected locally, stored locally at -80C and shipped on dry ice to Biorep at monthly intervals.

DNA and DNA derived from lymphoblastoid cell lines will be used (1) to confirm the presence and the size of the CAG expansion mutation within the HD gene for research purposes only, and (2) to identify genetic modifiers of HD, in particular genetic modifiers of age of onset, rate of progression and phenotypic characteristics presentations. For this purpose, one tube of ACD blood will be collected for the extraction of DNA, the generation of lymphoblastoid cell lines and the cryopreservation of lymphocytes. This will be required at the first visit only.

Plasma samples will be collected in EDTA tubes (3 × 6ml) for proteomic, ELISA and meso-scale analysis, and lithium-heparin tubes (2 × 6ml) for metabolomic analysis.

Two PAXgene RNA blood tubes (2.5ml) will be collected for the isolation of RNA for microarray or other RNA biomarker analysis.

5.5.8 Cognitive assessment

5.5.8.1 Overview of the cognitive battery

Time required: 60 minutes total at study visit, including 30 minutes for the core battery and 30 minutes for the experimental battery component.

Summary

The goal of the Track-HD cognitive battery is briefly to assess cognitive function and relate findings to progression of disease and to motor/oculomotor, neuropsychiatric symptoms, functional/quality of life, imaging, and wet biomarker measures in the Track-HD study. To achieve this goal, the cognitive assessment includes:

1. A core battery (Table 7), based on evidence for sensitivity to pre-manifest and manifest HD, planned for maximal overlap with the Predict-HD study, and
2. An experimental battery (Table 8), based on a combination of expert input and evidence suggesting these as promising avenues of assessment for premanifest and early HD, but for which the existing evidence falls short. For example, these tests may look strong cross-sectionally but have inadequate longitudinal evidence, or they may tap aspects of function expected to be affected in HD but that have not been conclusively demonstrated to be sensitive in premanifest and early disease.

Core and experimental cognitive assessments will be performed annually.

The cognitive battery will consist of tests designed to be good markers of cognitive decline based on a meta-analysis of previous studies (from the HD Toolkit, a project headed by Julie Stout), as well as the initial data from the Predict-HD study (Jane Paulsen, PI). In both the HD Toolkit and in Predict-HD, effect sizes (ESs) are being computed both for the differences between premanifest or early HD and control subjects (cross-sectional) and for the rate of decline within premanifest or early HD



groups (longitudinal). The selection of the core set of cognitive tests is based on converging information from these two sources that indicates strong evidence of the largest effect sizes relative to other candidate tests. Additional tests are included in the experimental battery if they show promise for tracking currently unmonitored aspects of HD pathology.

Test name [<i>Abbreviation</i>]	Type of Test	Avg. Time (Min)	Longest Time (Min)
Trails A	Paper	2	5
Trails B	Paper	3	5
University of Pennsylvania Smell Identification Test [<i>UPSIT</i>]	Paper	4-5	10
Static Emotion Recognition [<i>Neg Emo</i>]	Computer	5	10
Symbol Digit Modalities Test [<i>SMDT</i>]	Paper	2-3	2-3
Stroop Word	Paper	< 2	< 2
Speeded Tapping	Computer	1.5	1.5
Self-Paced Tapping, 550 Pace	Computer	3	3
IQ Covariate (NART [London], ANART [Vancouver], DART [Netherlands], Echelle de vocabulaire (Raven, J.C., Court, J.H., & Raven, J. (1986).	Paper	2.5	4.5
Serial 3s	Digital audio recorder	0	0

Table 7 Core cognitive battery

Test	Type of Test	Avg. Time (Min)	Longest Time (Min)
Speeded Tapping with Cognitive Load	Computer	2	2
Self-Paced Tapping Pace, Alt Pace	Computer	3	3
Mindstreams Visuospatial Imagery (Egocentric Perspective)	Computer	3.5	9
Circle Tracing Task	Computer	5	5
Visual Array Comparison Task (WM)	Computer	2.5	5?

Table 8 Experimental battery of promising cognitive tests

Relationship of Track-HD Cognitive Battery to Predict-HD

The study design for Track-HD is being finalized almost simultaneously as the Predict-HD Cognitive Battery is undergoing significant modification in response to the availability of data from the first longitudinal analysis of Predict-HD cognitive data. Therefore, we have an opportunity to maximize the benefit of both studies by: 1) using the results from Predict-HD to inform the selection of tests for Track-HD; 2) developing a strategy that allows comparability between the cognitive assessment components of the two studies by identifying a set of cognitive tests to be used in an identical fashion in both studies; and, 3) by also using a non-overlapping set of

cognitive tests in each of the studies that will provide a platform to investigate additional tests that have not yet been vetted in adequate samples of longitudinal premanifest subjects. The logic behind the set of non-overlapping cognitive tests is as follows: Although Predict-HD and the HD Toolkit meta-analyses have identified some very promising markers of the progression of pathology in both premanifest and early HD, we are not yet satisfied that we have the optimal set of cognitive markers. We propose expanding the core battery by inclusion of a set of tasks that is likely to be nonredundant with the core battery of tests and that either 1) shows evidence of large effect sizes but with insufficient quantity or quality of evidence to be included in the core battery, or 2) taps an ability area or brain region that is expected to be affected in premanifest HD. Track-HD and Predict-HD can be used in parallel to examine the potential sensitivity of such promising but unproven tests.

Tests will be administered by paper and pencil in the case of standard clinical neuropsychological tasks, or by using (TBD-provisional) standardised Dell laptops with custom-designed software, a standardised tablet input device, and a custom-designed button box input device. Cognitive raters will be trained to criterion in person and then submit a videotape prior to testing their first participant (i.e., a videotaped standard administration is judged to be adequate by a member of the organizing committee).

Secondary factors that will influence the final battery will be:

1. whether some tests are too similar (i.e. redundant in terms of testing the same underlying skill as demonstrated by analyses of concurrently administered tests when such data are available)
2. test administration time
3. ease of translation into other languages
4. ease of conversion into an electronic format
5. minimal practice effects (e.g. alternative test forms available)

Sources of Performance Variability and Steps to Minimize these Effects

Many studies have demonstrated cognitive impairment and/or decline in both premanifest and early HD (Bates, Harper, & Jones, 2002; Paulsen et al., 2006). However, because changes are expected to be small in premanifest HD, we must deliberately reduce performance variability that is unrelated to the disease process. These include variations in intelligence, age, sex, education levels, fatigue, mood, unstandardised test administration, and unknown number of prior exposures to a given test. Variability in intelligence will be controlled for by covarying pre-morbid IQ estimates in the results. Age, education levels, and sex will also be covaried in statistical analyses. The effect of fatigue will be minimized by conducting cognitive assessment as early as possible in the study visit day, and will be controlled for by keeping the time of day of the assessments as stable as possible across subjects. The effects of variation in mood on assessments will be minimized by assessing depression symptoms and covarying total scores in the cognitive assessments. To guard against variations in the test administration, cognitive assessors will receive face-to-face training and annual reliability checks on videotape. Control for unknown numbers of exposures to the test will consist of asking participants to indicate whether any of the tests they receive are familiar, and also by restricting participants who participate in Track-HD from participating in Predict-HD.

The final battery is designed to maximise the ability to measure longitudinal decline in performance as HD pathology progresses with the long term goal of detecting discrepancies in rate of decline between treated and untreated groups in clinical trials.



The battery is also designed to take into account the secondary factors mentioned above and to take approximately one hour to administer.

Rationale for test selection

There is now strong evidence that cognitive function starts to decline in CAG-expanded individuals in the period prior to clinical diagnosis of manifest HD (i.e., in Premanifest HD). Compared to other areas of clinical assessment, cognitive assessment for premanifest and early HD has been well studied and a large quantity of evidence can be brought to bear on test selection. Therefore, whenever possible, tests for the cognitive assessment protocol were selected based strong existing evidence. In the HD Toolkit project, we have evaluated all such evidence for cognitive tests published since the 1993 advent of the highly reliable polymerase chain reaction test for the mutant huntingtin gene. We have quantified the cross-sectional and longitudinal effect sizes for pre-manifest and early HD, and these findings have been carefully considered and have influenced test selection.

The “gold standard” for establishing sensitive markers for clinical trials would be a longitudinal study (preferably of relatively short duration) in a Premanifest HD population. Longitudinal change in Early HD also suggests strong evidence of useful marker. However, a measure that reveals decline in Early HD may not be sensitive enough to pick up the more subtle declines that occur in Premanifest HD. Thus, Premanifest HD longitudinal data has the highest evidentiary value for establishing a measure as a potential indicator of treatment effects in clinical trials. Importantly, the Predict-HD study under the direction of Jane Paulsen, has generously shared pre-publication findings in pre-manifest HD on specific tasks. This made it possible to re-run meta-analyses to inform Track-HD using the very substantial amount of Predict-HD data to increase the quantity of evidence for test selection. In fact, Predict-HD has provided the bulk of the “gold standard” evidence (longitudinal decline in premanifest HD) for cognitive test selection of a core battery for Track-HD. A unique contribution of the Predict-HD study is that, because of the co-administration of a large battery of tests, it was possible to examine the redundancy in the test battery in the amount of variance accounted for in estimated proximity to onset. This allowed us to take some steps to eliminate tasks that may be reliable markers of an aspect of HD progression that is already tracked by another measure.

Scientific questions for the cognitive battery. When is the earliest time-point that cognitive changes can be detected? What is the most sensitive set of tests for tracking cognitive change in pre and early HD? What is the nature and rate of change in cognitive function across time? What role do cognitive measures have in potential clinical trials of pre-manifest and early HD? What is the unique predictive contribution of cognitive function beyond what is provided by other assessment domains (other clinical markers and biological markers)?

Additional considerations

As described above, factors such as age, education, gender, fatigue, and mood are known to influence performance on many tests and need to be taken into account in data analyses. Since premorbid differences in IQ also affect cognitive performance (independent of disease progression) the inclusion of a brief IQ estimation test in the protocol is essential. Finally, practice effects are common in cognitive tests, and in some cases may reduce the sensitivity of tasks used longitudinally. Therefore, practice effects should be specifically considered in analyses and interpretation of these data.

5.5.8.2 Information on specific instruments

Trails A and B (Total time required: 5 minutes)

Participants execute the Trails A task by drawing a continuous line to connect a jumbled set of 25 circled numbers (1-25) in consecutive numeric order. Participants execute Trails B by drawing a continuous line that connects a jumbled set of 13 circled numbers (1-13) and 12 circled letters (A-L) into an interleaved, ordered series. In both tasks, participants are instructed to work quickly and the task is timed. Trails A is sensitive to deficits in sustained attention or information processing speed, but also requires visual scanning and psychomotor speed. Trails B assesses divided attention and cognitive flexibility in addition to the characteristics assessed by Trails A.

Likely main variable for analysis:

- Time to complete Trails A [sec]
- Time to complete Trails B [sec]

Rationale and strength of evidence for the selection of Trails A and B

HD Toolkit meta-analysis suggests that Trails B performance declines longitudinally in both Premanifest HD Near Onset and Early HD (Figure 10). In Premanifest HD, Trails B also provides unique ability to predict probability of onset within 5 years (Langbehn, et al., 2004) beyond that of the other tasks in the proposed core cognitive battery. Trails A, on the other hand, is not longitudinally sensitive in Premanifest HD Near Onset but begins to become sensitive in Early HD (Figure 10). Neither test reveals significant longitudinal change in Premanifest HD samples that include individuals far from estimated onset (>12 years.) Trails A is included in the core battery for two reasons. First, there is no data on the sensitivity of Trails B in the absence of prior administration of Trails A. Second, Trails A provides a psychomotor control for the Trails B task: If Trails B is sensitive but Trails A is not, this suggests the more executive aspects of the Trails B task are what is changing with disease progression.

Modified University of Pennsylvania Smell Identification Test (20 item subset of the UPSIT (UPSIT-20); Total time required: 5 minutes)

The original UPSIT is a 40-item test of olfactory function (Doty et al., 1984). In this “scratch and sniff” task, the participant is asked to identify the odour that was released by circling 1 of 4 choices. In the modified version recommended here, the number of items is reduced from 40 to 20. The reduction is based on a comprehensive analysis of the 2 year longitudinal sensitivity of this task in more than 500 Premanifest HD individuals from the Predict-HD cohort. Whereas the original test uses 4 books of 10 items each (books 1-4), the modified test uses only 2 books of 10 items each (books 1 and 3).

Likely main variable for analysis:

- Total number of correct responses.

Rationale and strength of evidence for the selection of UPSIT-20

HD Toolkit meta-analysis suggests that performance on the original UPSIT declines longitudinally in Premanifest HD Near Onset (Figure 10). In premanifest HD, the UPSIT also provides unique ability to predict probability of onset within 5 years (Langbehn et al., 2004) beyond that of the other tasks in the proposed core cognitive battery. When reduced to the 20 items in books 1 and 3, the longitudinal effect sizes in Premanifest HD are comparable to those of the 40 item test (Figure 7). In addition, the classification error rates for classifying individuals into subjects who are >15 years to expected onset (Far); 9-15 years to expected onset (Mid); < 9 years to expected onset (Near); and CAG-unexpanded based on the modified, 20-item UPSIT are comparable to the error rates for the original 40 item UPSIT (Figure 8). There is no UPSIT longitudinal data in Early HD but a cross-sectional study in Early HD

indicates that the UPSIT is one of the most sensitive cognitive tests in Early HD (Figure 10).

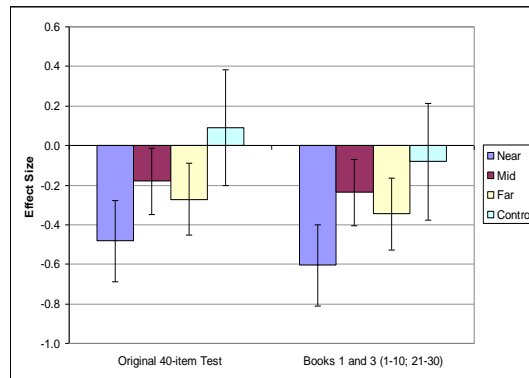


Figure 7 Effect sizes for modified UPSIT

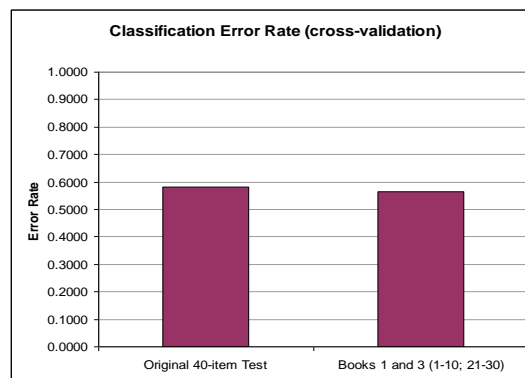


Figure 8 Classification error rates (near, mid, far from onset & control groups) for modified UPSIT

Static Emotion Recognition (Total time required: 5 minutes)

The Static Emotion Recognition task is designed to measure emotion recognition of static facial expressions (Ekman & Friesen, 1976). The participant views one of seven emotional facial expressions (anger, disgust, fear, happy, neutral, sad, and surprise) at a time on the computer screen for a maximum of 5 seconds. The participant responds to each expression by pressing one of seven touch screen buttons labelled disgust, fear, happy, neutral, sad, and surprise within 7 seconds of stimulus onset. The task includes 70 trials, 10 trials with each of the 7 emotional expressions.

Likely main variable for analysis:

- Total number of correct responses to the negative emotions of anger, disgust, fear, and sadness.

Rationale and strength of evidence for the selection of Static Negative Emotion Recognition

HD Toolkit meta-analysis suggests that performance on the anger faces in the Static Negative Emotion Recognition task declines longitudinally in Premanifest HD (Figure 10). However, all four negative emotions (anger, disgust, fear, and sadness) are impaired in the Predict-HD Premanifest HD cohort (Johnson et al., In press). Further, the Predict-HD team has shown that the sum of the correct responses to

negative emotions shows significant longitudinal decline in Premanifest HD (ES = -0.277) and provides unique ability to predict probability of onset within 5 years (Langbehn et al., 2004) beyond that of the other tasks in the proposed core cognitive battery.

Symbol Digit Modalities Test (SDMT; Total Time Required: 3 minutes)

This is a test of visuomotor integration, involving visual scanning, tracking, and motor speed. The examinee is given 90 seconds to match symbols and digits as quickly as possible. The key (specifying which number corresponds to each symbol) is located at the top of the page (Smith, 1991).

Likely main variable for analysis:

- Total number of correct responses.

Rationale and strength of evidence for the selection of SDMT

HD Toolkit meta-analysis suggests that SDMT performance declines longitudinally in both Premanifest HD Near Onset and Early HD (Figure 10). In Premanifest HD, SDMT also provides unique ability to predict probability of onset within 5 years (Langbehn et al., 2004) beyond that of the other tasks in the proposed core cognitive battery. A possible limitation of the SDMT is that, unlike the other tests in the core battery, some of the predictive ability of SDMT is due to practice effects in those far from onset, thus possibly limiting sensitivity of this test when far from onset participants are excluded from the study.

Stroop Word Test (Total time required: 2 minutes)

The Stroop Test has three conditions that require visual scanning, cognitive control and processing speed. Because the Word Reading condition (the first condition normally presented) is the most sensitive in premanifest HD, it is the only Stroop condition that will be used in the Track Cognitive battery. Subjects are given a card on which the names of colors are printed in black ink and must read as many words as they are able in 45 seconds.

Likely main variable for analysis:

- Number of words read correctly in 45 seconds

Rationale and Strength of Evidence

HD Toolkit meta-analysis suggests that performance on the Stroop Word Test deteriorates longitudinally in both premanifest (Predict-HD) and Early HD (Figure 10). Longitudinal studies are supported by a consistent pattern of results in cross-sectional studies of premanifest and early HD and sizeable correlations in premanifest HD with time to onset (ES=0.54, $p<.001$) and neuropathology/striatal volume (ES=0.35, $p<.001$); and in early HD with striatal volume (ES=-0.35, $p<.001$). Furthermore, in premanifest HD, Stroop Word provides unique ability to predict UHDRS motor score beyond that of the other tasks in the proposed core cognitive battery.

Speeded Tapping (Total time required: 3 minutes)

In each trial of Speeded Tapping, the subject places the non-dominant index finger on a button and presses the button repeatedly as fast as possible for 10 seconds. There are 5 trials. The Speeded Tapping provides a measure of motor speed and dexterity. This task provides several basic measures of tapping performance, which include (1) duration of each trial, in seconds; (2) mean inter-tap interval, in milliseconds; (3) standard deviation of inter-tap intervals, in milliseconds; and (4) coefficient of variation of inter-tap intervals



Likely main variable for analysis:

- Mean intertap interval.

Rationale and strength of evidence for the selection of Speeded Tapping

ESs from Predict-HD suggest that Speeded Tapping performance declines longitudinally in both Premanifest HD Near Onset (Figure 10) and also provides unique ability to predict probability of onset within 5 years (Langbehn et al., 2004) beyond that of the other tasks in the proposed core cognitive battery.

Speeded Tapping Cognitive Load (Total time required: 3 minutes)

A cognitive load is added to the Self-Paced Tapping task described above to increase difficulty and create a dual task condition in the hope of adding sensitivity to difficulties in multi-tasking thought to occur in Premanifest HD. In addition to tapping as fast as possible with the nondominant index finger, the participant will also perform the serial 3's task. In this task the participant starts at 100 and serially subtracts backwards by 3's, announcing each difference (e.g., 100, 97, 94, 91, 88, ...)

Likely main variable for analysis:

- Standard Deviation of the self-paced intertap interval.

Rationale and strength of evidence for the selection of Self-Paced Tapping

Although executive function is posited to be affected in HD and Premanifest HD, measures that tap this deficit have been difficult to find. Simple or well practiced motor movements such as walking are not impaired in healthy individuals when accompanied by a cognitive load. However, populations with executive function impairments (e.g., elderly) appear to lose motor automaticity and, consequently, their motor performance suffers when they simultaneously perform an additional cognitive task (cognitive load, Springer et al., 2006.) For example, gait variability in Parkinson Disease patients increases with cognitive load (Yogev et al., 2005) Therefore, adding a cognitive load to Self-Paced Tapping has the potential to improve the sensitivity of a task that is already somewhat sensitive to HD progression.

Self-Paced Tapping (Total time required: 3 minutes)

Self-paced tapping provides a measure of psychomotor functioning, including timing. The task begins with the repeated presentation of a tone at a constant rate. The participant is instructed to begin to tap with alternating thumbs at the same rate as the tone, when the participant feels that he/she has a sense of the timing. Once the participant begins to tap, the tone continues for another 12 taps, but is then discontinued. The participant will then attempt to maintain the timing of the tap for another 31 taps. This sequence is repeated 4 times for a total of 5 trials.

Likely main variable for analysis:

- Mean intertap interval.

Rationale and strength of evidence for the selection of Self-Paced Tapping

Effect sizes from the Predict-HD longitudinal database indicate that decline is only at trend level for this measure in Premanifest HD Near onset. However, we include this measure because 1) it was the only measure in Predict-HD that showed some evidence of sensitivity in those 9-15 years from onset, 2) we believe we can modify this task to make it more sensitive by changing the pace or by adding a cognitive load (see Speeded Tapping with Cognitive Load and Self-Paced Tapping Pace, Alternate Pace.)



Self-Paced Tapping Alternate Pace (Total time required: 3 minutes)

Identical to Self-Paced Tapping except with tones spaced every 360 msec.

Likely main variable for analysis:

- Standard Deviation of the self-paced intertap interval.

Rationale and strength of evidence for the selection of Self-Paced Tapping

Freeman et al. (1996) suggests that the sensitivity of Self-Paced Tapping might be enhanced by increasing the pace. Our pace of 360 msec is intended to maximize the pace for increased sensitivity but not exceed HD participants' maximum tapping speed (~4 Hz or one tone every 250 msec).

IQ Covariate (Total time required: 3 minutes)

The American National Adult Reading Test (ANART) (Gladsjo et al., 1999) and the National Adult Reading Test (NART-2) (Nelson & Willison, 1991) were chosen as estimates of IQ. Both the ANART and the NART-2 are 50-word tests that examine the pronunciation of phonetically-irregular words of varied culturally appropriate frequency (26 of the same words are included on both tests and 24 words on each test are culturally unique), thought to provide an index of the size of a person's vocabulary (Lezak et al., 2004) and a reflection of their premorbid level of intelligence. For Dutch, IQ will be estimated using the Dutch Adult Reading Test (DART; Bouma, Lendeboom, & Mulder, 1996), which is modeled on the NART and also consists of 50 irregularly spelled words which have to be pronounced correctly. For French, word pronunciation-based IQ estimates do not suffice because there are no comparable sets of irregularly spelled words; instead, the Echelle de vocabulaire Mill Hill will be used. For this test, participants are asked to judge pairs of words to determine whether they are synonyms.

Likely main variable for analysis:

- Estimated IQ score

IQ affects performance on a wide range of cognitive tests (Diaz-Asper et al., 2004). Thus, to assess appropriately the impact of brain injury or disease on cognition, estimates of premorbid IQ should be taken into account in the analysis and interpretation of cognitive data obtained from neurological populations. Data from Predict-HD have demonstrated that the ANART is generally superior to the two-subtest version of the Wechsler Abbreviated Scale of Intelligence (WASI) for estimating pre-morbid IQ in pre-HD (Carlozzi et al., manuscript in progress). Specifically, these data showed that ANART was less related to indices of disease progression (proximity to clinical diagnosis, difference from parental age at diagnosis, diagnostic confidence level and motor score) compared to the WASI.

Mindstreams Visual Spatial Imagery Task (Total time required: 3.3 minutes)

The Visual Spatial Imagery Test assesses abstract spatial ability. Participants are presented with a computer generated everyday scene containing a red pillar (rectangle) and instructed to imagine standing at this location. Four views of the scene are presented at the bottom of the screen and participants are required to indicate, using a keyboard number pad, which of the four views corresponds to the view of the scene from the location of the pillar. Within each of 16 trials, the stimulus is displayed until the subject responds or 90 seconds, whichever comes first.

Likely main variable for analysis

- Number of correct responses
- Total Response Time

Rationale and Strength of Evidence

In premanifest HD subjects, Rosas et al. (2005) found significant cortical thinning in the superior parietal lobe (Brodmann's Area 7). Some evidence suggests that this area is involved in the processing of egocentric visuospatial information related to development of goal directed actions (Sdoia et al., 2004). This cognitive domain has not been adequately assessed for sensitivity in Pre and Early HD. Therefore, the addition of such a test would further expand our knowledge and may extend our sensitivity farther from onset. Finally, this test has also been shown to be sensitive in Mild Cognitive Impairment (MCI) (Doniger et al., 2006).

Circle Tracing Task (Total time required: 5 minutes)

The Circle Tracing Task is designed to measure precision of motor movements that require continuous error feedback control (Lemay et al., 2005). The participant traces a 90mm diameter circle on a horizontal computer tablet while trying to remain within a 5 mm error margin that is indicated by a white annulus on a grey background. The participant first completes the task while directly viewing hand and stylus movement (3 trials, 45 seconds each.) The participant then repeats the task while indirectly viewing stylus movement on a separate, vertical computer screen with hand and stylus movement occluded from view (3 trials, 45 seconds each.)

Data generated for this task:

- Number of deviations per rotation in the indirect condition best differentiated Early HD from Controls.

Rationale and strength of evidence

HD Toolkit meta-analysis suggests that tracing tasks and movement to target tasks have promising cross-sectional effect sizes.

Note that Figure 11 illustrates the more traditional Cohen's *d* ES statistic. Because most of the studies of target tracing tasks have utilized relatively small sample sizes, however, we are also providing the ES statistic Hedges *g* in Table 9 which includes a correction for potential bias associated with small sample sizes.

	Cohen's <i>d</i>	Hedge's <i>g</i>
Boulet et al., 2005	-2.64	-2.53
Georgiou et al., 1997	-3.14	-3.03
Lemay et al., 2001	-3.55	-3.43
Smith et al., 2000	-1.68	-1.63

Table 9 Effect size comparison: Cohen's *d* and Hedge's *g*

That is, although based on limited data, the cross-sectional effect sizes for these tasks meet or exceed the cross-sectional effect sizes for those tasks in the core battery. In addition, the tracing and movement to target tasks likely tap an error correction mechanism that will likely have minimal redundancy with other measures in the battery. Circle tracing was chosen over the other tasks in this set because 1) the set-up did not require specialized robotics, 2) the time for the task was under 5 minutes, and 3) the sensitive dependent measure was computationally simple. (Note that although Ghilardi (2003) has a nice effect size in longitudinal Premanifest HD, the reference is only a letter and does not provide sufficient detail for task implementation.)

Visual Array Comparison Task (Total time required: 2.5 minutes)

This task assesses the ability to sustain object and location representations without the aid of rehearsal and chunking strategies, leaving a purer measure of attentional capacities. This task is thought to be sensitive to a critical bottleneck for executing perceptual and cognitive functions that occurs when it is necessary to extract and retain items in visual short-term memory (on average about 4 items).

On a given trial of the Visual Array Comparison Task (Cowan, 2001; Cowan et al., 2005; Luck & Vogel, 1997), an array (Figure 9) of coloured squares (4 or 8) is presented for 250 ms (short enough so that subjects cannot verbally encode the items). After 1000 ms a similar array is presented with one of the squares encircled. Subjects decide whether the square within the circle is the same as in the original array or has changed in colour.

Data Generated

- discriminability and bias indices
- Cowan's (2001) K formula for estimating the number of items encoded at each set size

Rationale

Cowan et al. (2005) found that tasks of this type correlate well with other working memory (WM) measures, and with G_F and other aptitude tests ($r = 0.31 - 0.52$). Cowan suggests that the task assesses individual differences in the flexibility of the scope of attention, such that higher WM individuals are able to “zoom out” to apprehend and sustain more items from the visual field. Unlike the greater activity typically observed in the lateral prefrontal areas during performance on traditional WM tasks, recent evidence suggests that neural activity associated with the capacity of sustaining conjunctive object/location information in this type of task is most strongly observed in the posterior parietal and lateral occipital areas (Todd & Marois, 2004, 2005; Vogel & Machizawa, 2004; Xu & Chun, 2006). Furthermore, the magnitude of this activity is predictive of individual differences in the number of items that can be retained (Todd & Marois, 2005; Vogel & Machizawa, 2004).

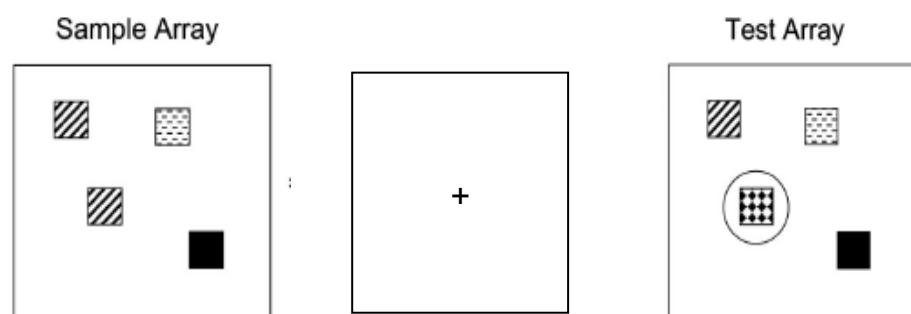


Figure 9 Sample trial for Visual Array Comparison Task

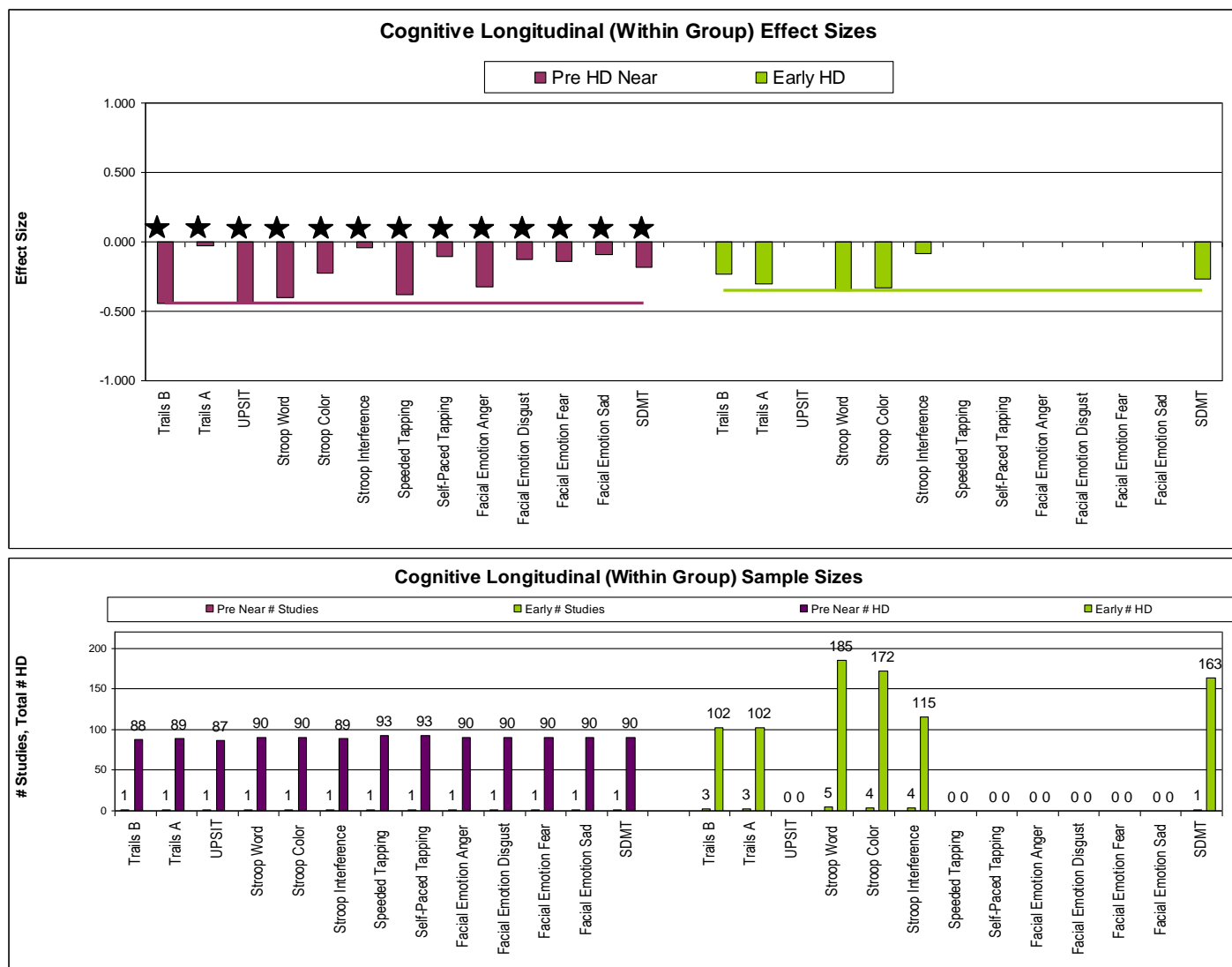


Figure 10 Cognitive Cross-sectional Effect Sizes (and Sample Sizes) from HD Toolkit
(Star indicates ES based solely on Predict-HD data)

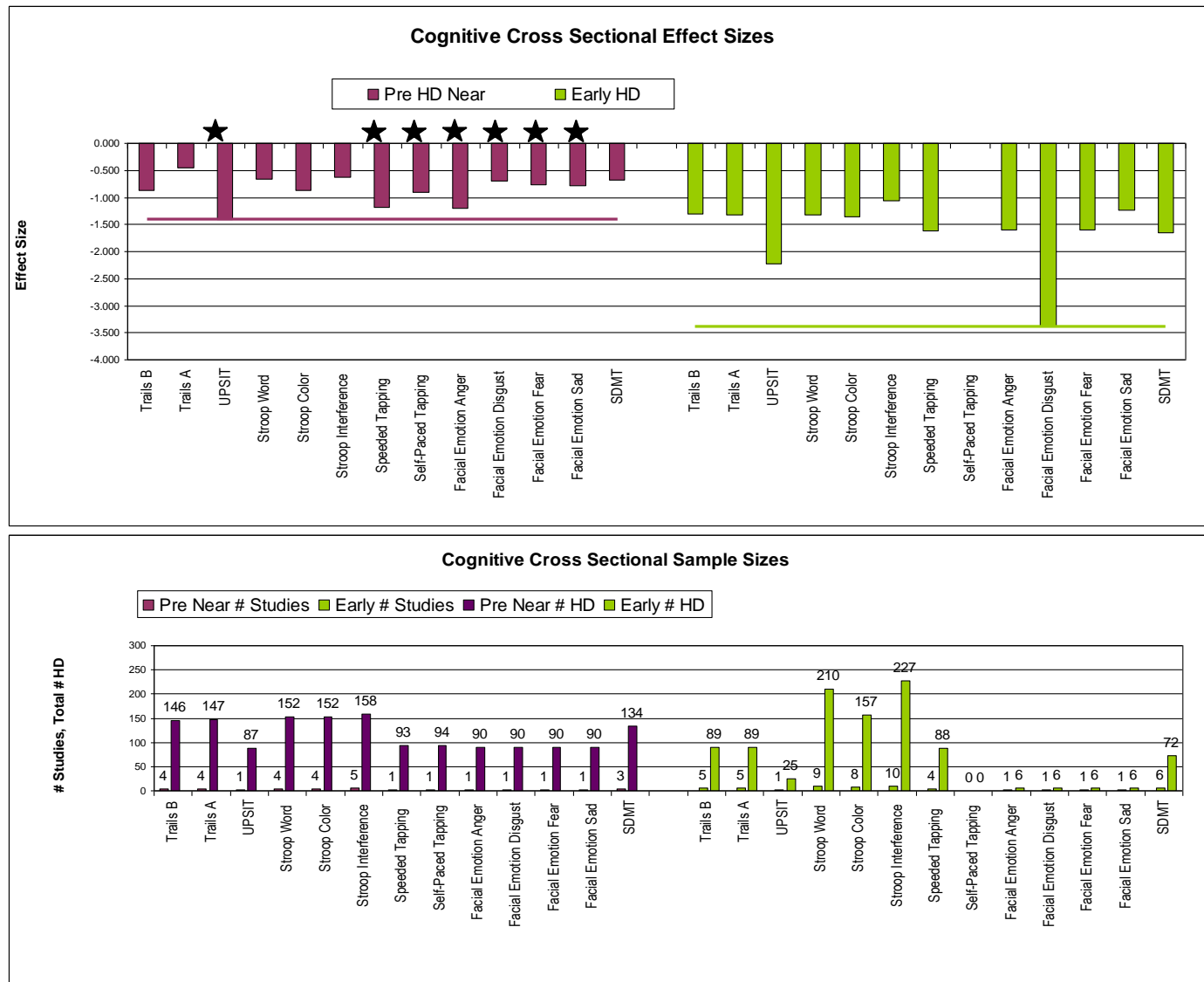


Figure 11 Cognitive Cross-sectional Effect Sizes (and Sample Sizes) from HD Toolkit
(Star indicates ES based solely on Predict-HD data)

5.5.9 Quantitative motor assessment

5.5.9.1 Overview and rationale for task selection

Motor dysfunction is a prominent sign of HD, and evidence from the UHDRS motor assessment in studies such as Predict-HD and multiple neurophysiological studies demonstrates conclusively that motor signs begin to develop well in advance of disease diagnosis. Yet, standard clinical assessment procedures such as the UHDRS motor exam exhibit limited sensitivity and reliability, which limits their capability to detect disease progression and impact of treatment. The goal of the quantified motor assessment component of Track-HD is to test a set of quantitative neurophysiological motor measures that use objective and precise measurement techniques, with the hope of both improved reliability and sensitivity, for tracking progression in premanifest and early HD.

Six quantified motor measures were selected, on the basis of expert input from Ralf Reilmann, Peter H. Kraus, and the EHDN Motor Working Group, for inclusion in the Track-HD protocol, as well as a review of existing studies: a) isometric tongue force analysis; b) isometric grip force analysis; c) finger tapping using the isometric force transducer; d) gait testing; e) posturography using a force-plate; f) neurophysiological chorea analysis and g) and graphimetry using a simple paper-and-pencil drawing and tracing task. These measures allow for a multimodal motor assessment of the key motor systems in brainstem, upper- and lower extremity, and bradykinesia using sophisticated gadgets as well as a simple, easy to administer tracing task (graphimetry). Although some data exists for some of these tasks that could provide evidence regarding possible effect sizes, with the exception of several gait studies and one posturography study, these data were not available at the time the protocol was developed and should be given further consideration as soon as is feasible.

Test	Measurement / Analysis
Brainstem motor coordination test	tongue force analysis
Upper extremity motor coordination test	isometric grip force analysis
Bradykinesia test	finger tapping with isometric force transducer
Neurophysiological chorea analysis	Using Polhemus 3D sensor
Gait test	analysis of normal pace and fast paced stride, and stride with mental distraction
Posturography test	lower extremity motor coordination force plate
Graphimetry	deviations in hand-tracing of a drawing (e.g., a spiral) on paper forms

Table 10 Quantitative motor measures

5.5.9.2 Equipment required per site

- A. One Multimodal Force Assessment System (supplied by laboratory of Ralf Reilmann, MD) including:
 - Personal computer with monitor or laptop equipped with extension for three serial ports (DB-9 standard) running a Windows operating system and pre-installed data acquisition system ZOOM/SC for Windows (licensed to Ralf Reilmann for use in TRACK-HD).
 - One pre-calibrated force transducer Mini-40 and amplifier (force transducer can be exchanged easily between tongue-force-, grip-force-, and tapping device by the investigator)
 - One Polhemus 3D-position sensor system including one transmitter and one receiver

- One platform for tongue force measurement
 - One two-finger grip device
 - One finger tapping device
- B. One GAITrite stride analyzer system for gait analysis
- Stride analyzer system
 - Digital audio recorder
- C. One force-plate for posturography including software
- D. One graphimetry test set (supplied by the laboratory of Peter H. Kraus. MD) including the following:
- a set of bar -code labelled sheets of paper with an imprint of the spiral to be traced in light blue ink
 - a ballpoint-pen
 - a stop watch
 - a high quality scanner (Hewlett-Packard, Typ: HP Scanjet 7400C; resolution 200dpi – black/white) and an appropriate PC running custom made data analysis software using Visual Basic 6.0 and Matlab 6 is required for rater-independent, fully computerised data analysis.

5.5.9.3 Information on specific tests

Brainstem motor coordination test (isometric tongue force variability) (Total time required: max. 10 min)

This task assesses the coordination of tongue protrusion forces (named “glossomotography”). Tongue force is measured using a specially designed setup (Figure 12): a force transducer is mounted on a height adjustable base located on a table. The force transducer is interfaced with a personal computer using the flexible data acquisition system ZOOM/SC (University of Umea, Sweden). The laboratory of Dr. Ralf Reilmann has obtained special limited licences for use in the setting of this study. Programs written in a special SC language for data acquisition are supplied by Dr. Reilmann’s laboratory.

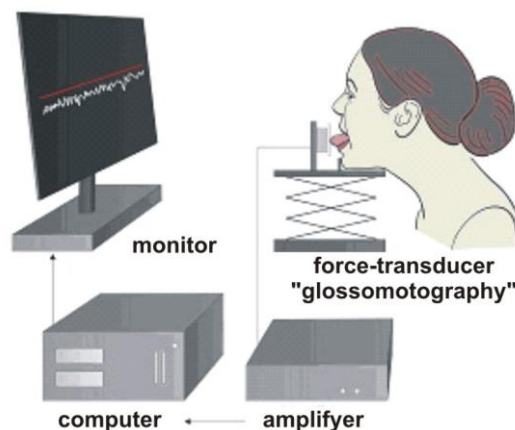


Figure 12 Tongue force apparatus

The primary outcome measure “tongue force variability” was shown to be severely impaired in patients with HD compared to controls and was correlated to UHDRS-TMS and CAG-repeat length when normalized for the age of patients (Figure 13).

Impairments in “tongue force variability” were also found in premanifest carriers of the Huntington gene (Reilmann, personal communication).

Participants are asked to place her/his chin on the base of the assessment system. Following a cueing tone, participants are instructed to protrude their tongue, press on the force transducer and generate different force levels presented as feedback on a monitor in front of them (0.25 N, and 0.5 N). Five 20 second trials are performed in each condition. Isometric tongue protrusion forces are recorded. The subjects should be instructed not to bite on their tongue while protruding the tongue. If subjects retract the tongue they should be asked to try to protrude it again and continue to press on the force transducer for as long as possible while the trial is running.

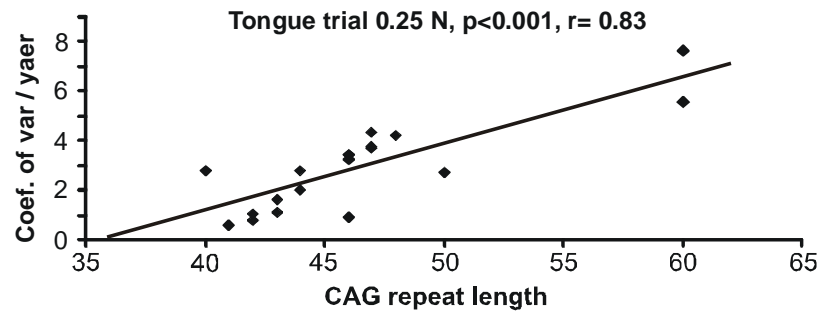


Figure 13 Correlation of tongue force variability to CAG repeat length

Data generated for this task includes, for each trial:

1. tongue force variability (primary outcome measure) [%]
2. mean tongue force [N]
3. mean contact time [sec]

Upper extremity motor coordination test (isometric grip force variability) (Total time required: 5 min).

This task assesses the coordination of isometric grip forces in the precision grip between the thumb and index finger during grip initiation, object transport and in a static holding phase. Grip forces and object position are measured using a grip device (Figure 14), equipped with a pre-calibrated force transducer measuring grip (normal) and lift (vertical) forces and a Polhemus 3D position sensor measuring x-, y-, z-position and roll-, pitch-, yaw-orientation of the object to assess object movement.

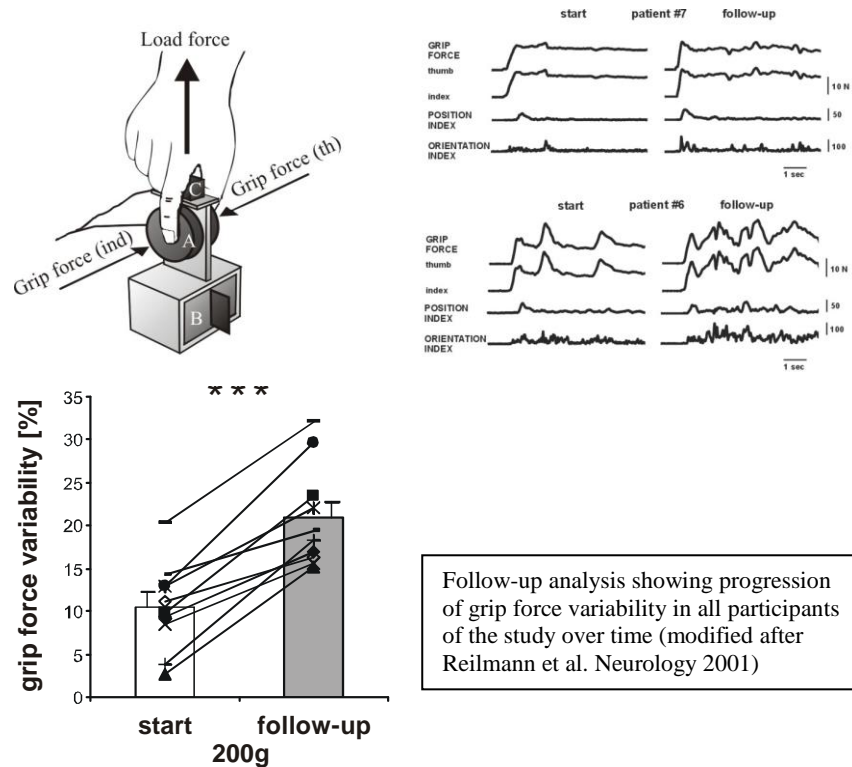


Figure 14 Grip force apparatus, sample recordings & follow up analysis

The force transducer and Polhemus are interfaced with a personal computer using the flexible data acquisition system ZOOM/SC (University of Umea, Sweden). The laboratory of Dr. Reilmann has obtained special limited licences for use in the setting of this study. Programs written in a special SC language for data acquisition are supplied by this laboratory. The coordination of grip forces including the timing and variability of force generation and amount and the impact of involuntary choreic movements (3D data) are measured and analysed (detailed list of variables see below).

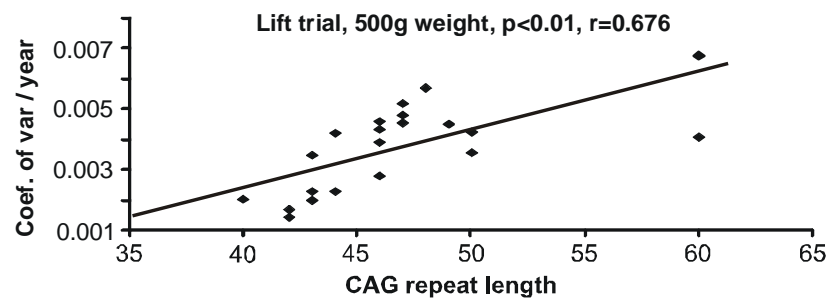


Figure 15 Correlation of grip force variability to CAG repeat length

Impairments in grip force coordination in HD were described by many groups (for review see Reilmann 2004). Using the paradigm described in this protocol, “grip force variability” was correlated to the UHDRS-TMS (Gordon et al. 2000) and showed progression in a follow-up study (Reilmann et al. 2001). Recent studies showed that “grip force variability” was also correlated to CAG-repeat length when normalized for the age of patients (Figure 15) and that deficits can also be found in premanifest carriers of the Huntington gene (Reilmann 2004 & pers. comm.).

Participants are seated in front of a table with their wrist resting on the edge of the table and the grip-device placed 30 cm away from the edge of the table in front of them. Patients are instructed to grasp the grip device at a comfortable speed after a

cueing tone signals the start of the trial. They are instructed to lift the device and hold it stable next to a marker made up by a wooden block, 10 cm high. A second cueing tone signals the end of the trial 30 seconds after the first tone, at which patients are instructed to replace the device at comfortable speed on the table, release the grip and return the wrist to the resting position before initiation of the next trial. 5 trials are performed with each hand.

Data generated for this task includes, for each condition:

1. mean static grip force variability (primary outcome measure) [%]
2. mean static grip force [N]
3. maximal grip force [N]
4. maximal grip force rate [N/s]
5. maximal load force rate [N/s]
6. preload phase [msec]
7. load phase [msec]

Finger Tapping with Force Transducer Task (Total time required: 5 min)

For this task, a force transducer is attached to a base located on the table 30 cm in front of the participant (Figure 16). Following from the design of the finger tapping test used in the Predict/Track core battery, and based on the findings from the Predict data showing that non-dominant hand finger tapping shows the greatest sensitivity within the Predict cognitive battery, the design of the Finger Tapping with the force transducer task is similar as the one used in Predict-HD. For each trial, participants will be instructed to use the non-dominant hand, and to tap as quickly as possible from the time a first auditory signal is sounded until a second one is sounded 10 seconds later. Each participant will complete six 10 second trials.

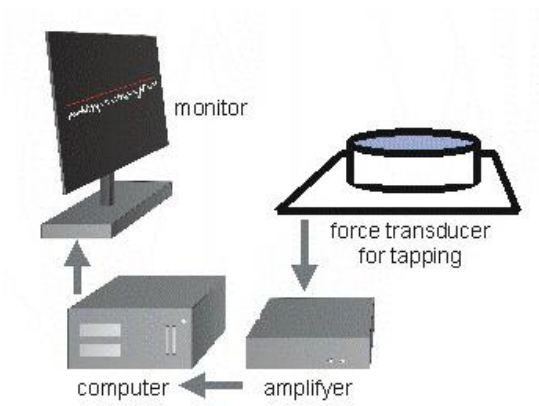


Figure 16 Finger tapping force apparatus

Data generated for this task includes, for each trial:

1. tapping rate (primary outcome measure) tapping rate (primary outcome measure) [n]
2. tapping rate variability [%]
3. tapping intensity
 - a. normal force applied [N]
 - b. maximal force generation rate [N/s]
 - c. inter tap interval [sec]



Rationale for test selection

The Finger Tapping Test is sensitive in Premanifest HD near onset in the Predict-HD database, and has the largest longitudinal effect size for all measures in the cognitive battery for Predict-HD. The addition of the force-related variables may enhance the sensitivity of the test. In Track-HD, we include both the Predict-HD version for the purpose of replication and because we wanted to ensure the best chance of replicating the substantial longitudinal effect size, and we add this force transducer-based version to allow examination of the comparability and relative sensitivity of the two task formats—this will be invaluable for informing future studies.

Gait Analysis (Total time required: 15 min)

This task assesses properties of the patient's gait. The patient walks across a carpet that is embedded with sensors which record foot strike timings (and positions). From these data the system calculates gait variables such as stride length, cadence, and % of time in double support, along with coefficients of variation (within patient) for these same variables. Data acquisition and calculations of gait variables are performed by the GAITrite system which is interfaced to a Windows based computer program specifically designed for assessment of gait using the GAITrite mat and installed on the assessment computer.

For this task, a specially manufactured mat, 4.3 meters in length, is rolled out in a clinic hallway, with at least 3 meters at either end. Participants will be asked to walk back and forth across the mat for four lengths total in each of 3 conditions:

1. Walk back and forth (4 lengths) at normal speed
2. Walk back and forth (4 lengths) at fast speed
3. Dual task-walk back and forth (4 lengths) while continually performing the serial 3s task (i.e., counting backwards by 3s) or a similar task. Performance of the serial 3s task will be audio recorded in addition to recording the gait variables.

Data generated for this task includes, for each trial:

1. Velocity
2. Cadence
3. Stride length
4. % Time in double support
5. Coefficient of variation in velocity
6. Coefficient of variation in cadence
7. Coefficient of variation in stride length
8. Coefficient of variation in % time in double support
9. Serial 3's accuracy score

Rationale for test selection

The HD Toolkit project retrieved 7 published articles reporting cross sectional differences between controls and HD patients (some only in late HD) in gait analysis variables as well as 1 published abstract reporting gait differences between controls and preHD individuals. Meta-analysis across studies suggested HD and preHD individuals performed worse than controls. The largest cross sectional effect sizes across the various measures range from -0.6 standard deviations of difference

between controls and preHD to -1.4 standard deviations of change between controls and early or late HD (see Table 11: Data are from Bilney, 2005; Churchyard, 2001; Delval, 2006; Hausdorff, 1998; Rao, 2005; Rao, 2007; Reynolds, 1999; Thaut, 1999).

Measure	PreHD (r =Correlation w/ Expected Onset)	EarlyHD	LateHD
Velocity	r = -0.65 ES = -.77 1/15	ES = -0.97 3/23	ES = -1.26 4/81
CV Speed		ES = -0.84 1/15	
Cadence	r = -0.7 1/15	ES = -0.69 2/17	ES = -0.80 4/82
CV Cadence	ES = -0.58 1/15	ES = -1.36 2/27	ES = -1.23 1/20
Stride Length	ES = -0.68 1/15	ES = -1.38 2/17	ES = -1.08 3/62
CV Stride Length	ES = -.77 1/15	ES = -1.07 1/15	
% Time Double Support	ES = -0.61 1/15	ES = -1.00 2/17	ES = -0.42 3/69
CV Double Support		ES = -1.43 1/15	ES = -1.41 1/19

Table 11 Effect Sizes for Gait

(Note: 4/81 indicates 4 studies with 81 subjects)

Posturography for lower extremity motor coordination test (force plate) (Total time required: 5 min)

This task assesses the balance of patients, which is dependent e.g. on lower extremity and trunk motor coordination. Position of the centre of mass is calculated using the input of three different integrated and pre-calibrated force transducers mounted in the force plate (Figure 17). Data acquisition, presentation and evaluation are performed by a Windows based computer program called “SATEL” specifically designed for the force plate and installed on the assessment computer.

Assessment will be performed with visual feedback (eyes-open) and without visual feedback (eyes closed). The force plate should be placed next to a table or wall and the examiner should be next to the patient to prevent falls. Applicability of the force plate in HD has been demonstrated previously (Tian et al. 1991). Correlation of variables to the UHDRS-TMS was seen recently (Reilmann, pers. comm.)

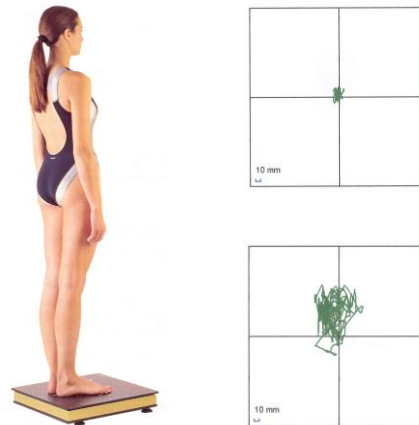


Figure 17 Posturography apparatus

Patients stand in front of the force plate bare feet. They are instructed to step on the force plate and place their feet in a marked position. Investigators verify that patients are in the right position prior to starting the assessment. They will be instructed to stand still as well as they can for a period of thirty seconds. Recording is initiated after a verbal instruction (“start”). A bar on the computer screen indicates the remaining time until the end of the trial. The investigator will indicate to the patient that the recording time is finished by saying aloud (“end”) and verify the patient’s position before initiating the next trial. The patient should perform the task 3 times in two different conditions: eyes open and eyes closed.

Data generated for this task includes, for each trial:

1. surface area [mm^2] (primary outcome measure)
2. distance moved [mm]
3. velocity [m/sec]

Rationale for test selection

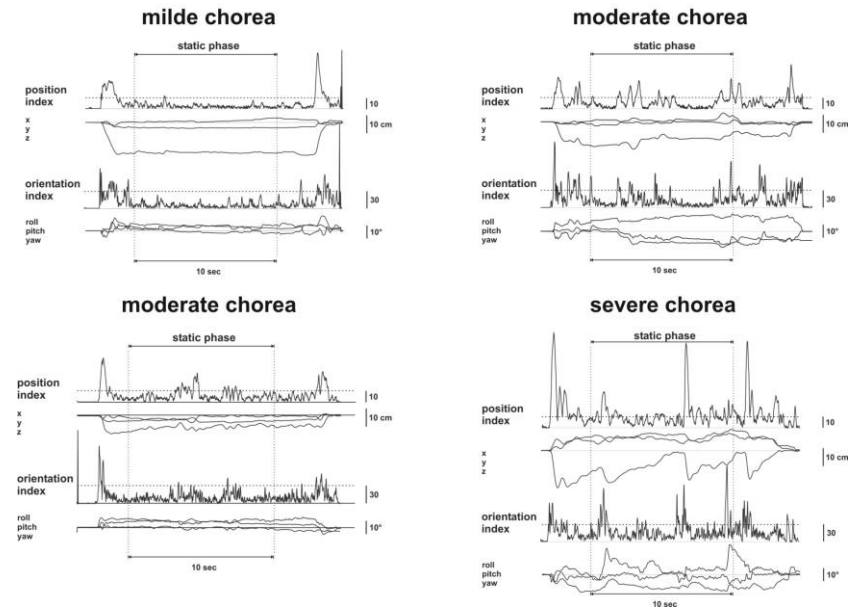
In addition to the unpublished work from Ralf Reilman’s laboratory, the HD Toolkit project found 3 published articles reporting cross sectional data on posturography in HD populations. One article is still being retrieved. The Tian (1991) article had insufficient data to compute accurate effect sizes, but approximate cross sectional effect sizes suggest controls performed 0.6 to 0.8 standard deviations better than HD patients of unspecified extremity. In addition, a Tian (1992) article reports controls performing 1.6 to 2.1 standard deviations better than 20 late HD patients. Unfortunately, there was no published data on posturography in early or preHD.

Neurophysiological analysis of involuntary choreatic movements (acquired from grip force task – no additional time needed)

During the upper extremity motor coordination test with the grip device, 3D position (x, y, z) and orientation (roll, pitch, yaw) are recorded objectively and quantitatively. Patients are instructed to hold the object stable next to a marker and involuntary choreatic movements interfering with this task are recorded. Mathematical analyses of the deviations occurring during the static holding phase provide the derived measures “position-index” (sum of absolute values of first derivatives of x-, y-, and z-channels) and “orientation-index” (sum of absolute values of first derivatives of roll-, pitch-, and yaw-channels) (Figure 18). The analysis was used to objectively assess the impact of chorea on other motor tasks in previous studies (Reilmann et al. 2001). Both measures were shown to be correlated to UHDRS-TMS chorea scores (Reilmann 2004) (Figure 19).

Data generated for this task includes:

1. position-index
2. orientation-index



Samples of several patients with different degrees of severity

Figure 18 Objective quantitative analysis of chorea

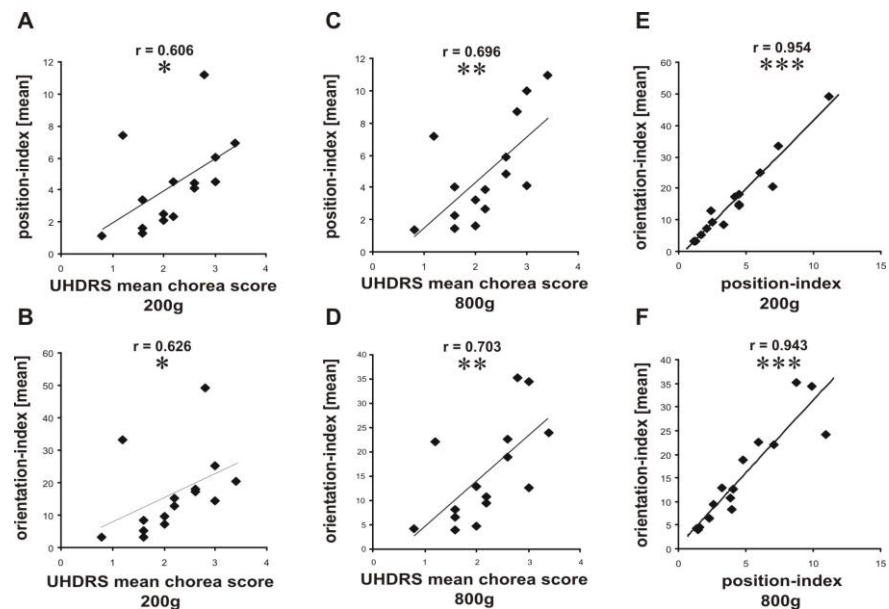


Figure 19 Chorea indices are correlated to UHDRS and to each other

Graphimetry for upper extremity motor dexterity test (Total time required: 2 min)

For the graphimetry task, participants are given a bar-code labelled sheet of paper with an imprint of the spiral to be traced displayed in light blue (Figure 20). Participants are instructed to trace the spiral as accurately as possible, using a black ball-point pen, without lifting the pen off of the paper. Each spiral is traced once with each hand. Instructions are given both verbally and by examiner demonstration. Tracings are completed at each annual study visit, and are timed by stopwatch. In addition, participants are asked to complete tracings at home at fixed intervals (immediately after the visit daily for 5 days, and then monthly beginning one month after the study visit (month 2) until month 11. In total there are 16 at home repeats of the task during each six month interval, and one instance per year during the study visit. Sampled forms are then sent to the evaluation centre; participants are given a new set of forms, and asked to repeat the same intervals as above. Scoring of graphimetry task performance is accomplished by digitising the forms using a scanner, and then transferring the electronic data Peter Kraus's laboratory in Bochum, where customized automated software is used by an study independent IT-specialist for data analysis (Figure 21).

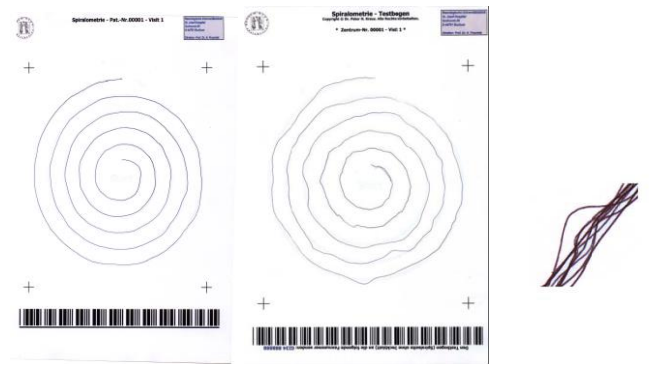


Figure 20 Graphimetry tracing example

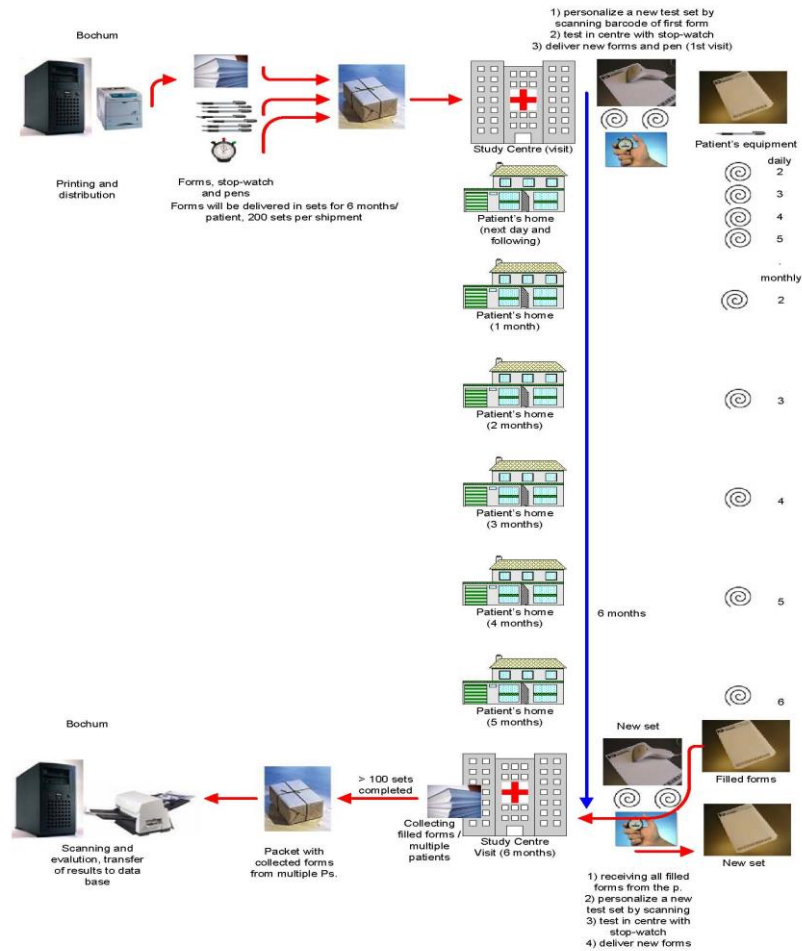
Main variables to be analyzed for each trial include:

1. deviations from target trace [mm] (primary outcome measure)
2. surface area of deviations from target trace [mm²]
3. Time to complete tracing [sec]

Rationale for test selection

The graphimetry task was included on the basis of expert input (Bernhard Landwehrmeyer, Peter Kraus) and the existence of some preliminary evidence for sensitivity in pre-manifest and early HD. Although ESs have not yet been computed to allow the magnitudes of these associations to be compared with other quantified motor or clinical outcome measures, results in a cross-sectional study (55 HD mutation carriers in various stages of HD (0 – IV) and in 32 controls) suggested a good separation of controls and stage 0 mutation carriers as well as increasing tracing deviations in stages I – III; since evaluation was optimised for early diagnosis a ceiling effect was observed at stages III-IV. A correlation to chorea of the upper extremities as assessed by the UHDRS motor score was established (Landwehrmeyer, personal communication). The graphimetry test has many potential advantages: is very brief, repeatable, and adaptable to telemedical data acquisition. The ease of application permits frequent data collection so that day-to-

day variability can be used to establish a rational basis for optimizing sampling frequency for future study. In addition, graphimetry data can be compared to other quantitative motor tests to determine to what extent graphimetry results can predict results obtained with quantitative motor test requiring sophisticated equipment.



(Diagram showing a six-month period after initial visit)

Figure 21 Schematic of graphimetry digitized scoring

5.5.10 Imaging assessment

All subjects will undergo T1 and T2 MRI at every visit on 3T scanners. Protocol details will be provided in the Track-HD SOP documents. This modality was chosen because it can provide images suitable for the most widely used and discriminating analysis techniques. (Aylward et al., 2004; Henley et al., 2006; Rosas et al., 2005; Kassubek et al., 2004) Ultimately, all imaging data will be collected, quality-controlled, stored, distributed and analysed through the imaging CRO and HDNI.

3T MRI scanners have been chosen for Track-HD, for the following reasons:

- All the planned image analysis techniques can be applied to 3T scans;
- There is better grey-white definition for the same scan duration.
- 3T scanners are using cutting edge technology and as new imaging techniques become available, the 3T MRI collection from TRACK-HD will be invaluable

for further analyses in the future, in addition to the morphometric studies planned for TRACK-HD.

- 3T imaging represents technology that will become dominant, which means that TRACK-HD is undertaking an imaging protocol which will be at the forefront of research and trials.
- All main centres with MRI facilities will be changing to 3T scanners, and this is currently occurring at a rapid pace. In ~3 years' time when the planned HD clinical trials occur, it is likely that there will be enough good HD clinical centres throughout Europe who will have access to a 3T scanner to make a clinical trial in excess of 500 patients viable.

A subset (25%) of all 3 groups of subjects, chosen according to patient willingness and consent to having 2 separate scans, will also undergo same-day volumetric scanning at baseline and 12 months on 1.5T scanners. This will allow cross-scanner comparisons to be performed so that the degree to which the 3T findings of Track-HD apply to 1.5T scans can be calculated.

The following image analysis will be performed by specified experts upon successful application to the Track-HD Steering committee:

- 1) Whole brain volume and rates of brain atrophy and caudate volumes (BBSI) (Freeborough & Fox, 1997)
- 2) Cortical thickness (Freesurfer - <http://surfer.nmr.mgh.harvard.edu/>) (Rosas et al., 2005)
- 3) Voxel-based morphometry (VBM) (Ashburner & Friston, 2000)
- 4) Automated segmentation of regions of interest including caudate and putamen (BRAINS (Brain Research: Analysis of Images, Networks, and Systems) is a software suite that integrates reliable and validated image analysis tools for large neuroimaging studies.

In addition, Track-HD and High Q support the widest possible use of these data for scientific purposes. The full imaging datasets will therefore be made available for legitimate research purposes on request subject to agreement of the steering committee. For full details on Data sharing, see section 5.19.2.

5.5.11 Oculomotor assessment

5.5.11.1 Overview and rationale for task selection

Changes in parameters of rapid eye movements (saccades), such as inability to suppress reflexive saccades and delayed initiation of voluntary saccades, are one of the earliest markers of Huntington's disease (Lakse & Zee, 1997). The cortico-basal systems that underpin voluntary eye movement significantly overlap the neural degeneration associated with HD, and it is not surprising that eye movements are a sensitive indicator of the associated cognitive and motor impairments.

There have been a number of recent publications correlating saccadic parameters such as latency, velocity and error rate with numerical indicators of HD progression (UHDRS score, or as a function of CAG repeat length x Age). The Track-HD oculomotor test battery incorporates the effective components of these studies.

Ali et al. (2006) reported a significant increase in mean saccadic latency for a reflexive task, and upon further analysis showed a significant increase in the proportion of early saccades in Early HD patients compared to premanifest HD gene carriers. The strength of this result was sufficient to permit a 75% accurate

prediction of HD status. This strength was due to the high number of repeated trials (300) and a sophisticated latency analysis technique called LATER modelling (Reddi & Carpenter, 2000).

Various voluntary saccade paradigms have been reported as having good correlations with HD progression. Blekher et al. (2004) & (2006) showed an increase in mean saccadic latency in voluntary saccade tasks. Golding et al. (2006) supported this finding and reported an increase in latency *variance* that correlated linearly with HD progression.

The anti-saccade paradigm is a successful predictor of HD progression, with saccade latency and error rate correlating positively with HD progression (Blekher et al., 2004, 2006). Recently, Rivaud-Perhous et al. (2007) reported that tests with mixed pro and anti saccades have even greater power when compared to performance in single tasks (of either pro or anti saccades). The mixed paradigms increase cognitive demand by requiring the participant to switch between rules. Repeated trials (e.g. two prosaccades) may be compared with switch trials (prosaccade preceded by an antisaccade), providing data on the participants ability to switch between rules, as they inhibit the previous instruction and apply a different rule. In Rivaud-Perhous et al. (2007) study, HD patients were not tested, but patients with cortico-basal degeneration had the strongest effect of the mixed pro-anti paradigm. HD deficits in rule-switching are also reported elsewhere (Aron et al., 2003).

List of tests Total time required: 30 minutes	Saccade types	Dependent variables and comparisons
Second Order Conditional Conflict task (SOCC) • cued choice paradigm	pro-saccades anti-saccades	Latency, velocity and errors for • pro-saccades in the reflexive vs the SOCC task • switch cost within the SOCC task
Baseline saccade latency and velocity	reflexive saccades	• pro-saccades vs anti-saccades

Table 12 Oculomotor assessments

5.5.11.2 Equipment required

- Personal computer with monitor, or laptop
- Saccadometer Advanced Eye Tracker (Ober Consulting)
- Software
- (2) AA batteries (spare)
- Desk & chair

5.5.11.3 Information on specific tasks

Second Order Conditional Conflict task (SOCC)

We successfully piloted a paradigm that combines the most effective elements above into a single paradigm. The main task is called the Second Order Conditional Conflict task (SOCC), which combines a pro/anti saccade task with a second condition, the shifting of the peripheral targets. The subject is presented with a central cue which is either Green or Red, denoting pro or anti saccade respectively, and a peripheral target that can appear either right or left. The central cue colour and the peripheral target location are varied randomly throughout the trial. The subject must interpret the central cue as a pro or anti

saccade condition and apply that rule to the target, producing a pro or anti saccade in either direction.

Reflexive Task

In addition to the SOCC task, the participants also perform a brief reflexive task where they must look rapidly from a central cue to a peripheral target which will appear left or right at random. This provides a baseline of saccade latency and velocity to which the SOCC scores can be compared.

Overview and rationale for oculomotor assessment session

These two conditions are administered in two blocks with an A-B, B-A presentation order, including a short rest break between blocks. Each block has 30 Reflexive trials and 70 SOCC trials producing a grand total number of trials of 200. The total testing time, including instruction and breaks is 30 minutes. The reduction in number of necessary conditions makes for a much simpler testing paradigm, and the large number of repeats is necessary to perform LATER model analysis.

Control subjects performed very well in this task, taking their time to consider the rules and generating a low percentage of errors. Premanifest participants took a significantly longer time to process the rules, made more errors and had a greater number of early (reflexive) saccades to target. Early HD participants made a significantly large number of early saccades to target with a substantially higher error rate, and in addition, also spent an even greater length of time processing the central cue. The linear relation of these three main factors appears to correlate well with disease progression.

5.5.11.4 Overview and rationale for selection of eye tracking hardware

The Eyelink II (SR Research) is a popular device for eye tracking and has been used successfully in a number of studies (e.g. Golding et al., 2006, Blekher et al., 2004, 2006). It has sufficient temporal and spatial resolution (up to 500Hz, and <0.5 degrees) for calculating saccadic latency and velocity. It automatically compensates for head movement, and is relatively easy to program. However it has two major disadvantages for a multi-site clinical study: its cost, and its reliance on a permanent connection to a PC.

In contrast, the Saccadometer (Ober Consulting) is a more appropriate choice of hardware. It is 1/10th the price of the Eyelink II, it has a faster temporal resolution (1000 Hz) and an equivalent spatial resolution. It is battery operated and hand held, with lasers mounted onto the front to project visual targets on almost any surface. This makes the Saccadometer free to be used in practically any room, as long as there is a clear wall available. Furthermore, because the visual targets are also head mounted, there is no need to compensate for head movement. In all, the Saccadometer is a far simpler solution to multi-site eye tracking, and at a fraction of the price it is the best choice for providing a systematic data collection environment.

The Saccadometer has been used successfully in an HD study (Ali et al., 2006) and other studies (Reddi & Carpenter, 2000). We have tested it extensively this year at Charing Cross Hospital and the Queen Square NHNN HD Clinic and have found it extremely easy to use. The data analysis software that comes included is sophisticated and efficient. Blinks and other erroneous eye movements are automatically excluded, and the onsite experimenter needs only to enter the Subject and Clinic ID before transmitting the recordings to the database. The data files produced by the Saccadometer are incredibly compact, < 500 kilobytes per

test, which will greatly facilitate the transmission of data between Track-HD sites.

5.5.12 Observation schedules

The observation schedule for Track-HD is as follows and assessments are represented in detail in Table 13

5.5.12.1 Visit 1 (Baseline)

- Review study with subject and obtain written informed consent
- Assign subject pseudonymous study number
- All subjects
 - Clinical
 - Neuropsychiatric
 - Cognitive
 - Quantitative Motor
 - MRI
 - Blood samples
 - Oculomotor

5.5.12.2 Visit 2 (12-month)

- All subjects
 - Clinical
 - Neuropsychiatric
 - Cognitive
 - Quantitative Motor
 - MRI
 - Blood samples
 - Oculomotor

5.5.12.3 Visit 3 (24-month)

- All subjects
 - Clinical
 - Neuropsychiatric
 - Cognitive
 - Quantitative Motor
 - MRI
 - Blood samples
 - Oculomotor



Table 13 Detailed assessment plan

PROCEDURE / CRF form	Visit 1 - Baseline		Follow Up		Follow Up	
	0 Months		12 Months		24 Months	
General	Participant	Companion	Participant	Companion	Participant	Companion
Informed Consent/In-Exclusion	X					
History (medical, disease, psychiatric)	X		X		X	
Invariable Demographic Data	X					
Co-morbid Conditions	X		X		X	
Concomitant Medication	X		X		X	
Family History	X		X		X	
CAG	X		X		X	
End of Trial						
Visits						
Variable Demographic Data	X		X		X	
Clinical History and Ratings						
UHDRS '99 TFC	X		X		X	
SF 36	X		X		X	
Quality of Life Index	X		X		X	
UHDRS '99 Motor	X		X		X	
Function	X		X		X	
Neuropsychiatric Assessment						
Short Behavioural Assessment - PBA	X		X		X	
Becks Depression Inventory Version II - BDI II	X		X		X	
Hospital Anxiety/Depression Scale - HADS	X		X		X	
Snaith Irritability Scale - SIS	X	X	X	X	X	X
Frontal Systems Behaviour Inventory - FrSBe (Pat)	X	X	X	X	X	X
Irritability Scale for Huntington's Disease - ISHD (7 days)		X	X	X	X	X
Biosample Collection						
Samples (DNA and LB lines at Baseline)	X		X		X	
ADC tube for DNA & lymphoblastoid cell line	X					
Cognitive Assessments						
Core Cognitive Battery	X		X		X	
<i>Trails A - B</i>						
<i>Smell Identification Test</i>						
<i>Static Negative Emotion Recognition</i>						
<i>Symbol Digit Modalities Test</i>						
<i>Stroop Word Test</i>						
<i>Speeded Tapping</i>						
<i>Self-Paced Tapping, 550 Pace</i>						
<i>IQ Covariate</i>						
Experimental Battery of Promising Tests	X		X		X	
<i>Speeded Tapping with Cognitive Load</i>						
<i>Self-Paced Tapping Alternate Pace</i>						
<i>Mindstreams Visual Spatial Imagery Task</i>						
<i>Circle Tracing Task</i>						
<i>Visual Array Comparison Task</i>						



PROCEDURE / CRF form	Visit 1 - Baseline		Follow Up		Follow Up	
	0 Months		12 Months		24 Months	
General	Participant	Companion	Participant	Companion	Participant	Companion
Quantitative Motor Assessments						
Quantitative Motor Assessments	X		X		X	
<i>Brainstem Motor Coordination Test</i>						
<i>Upper Extremity Motor Coordination Test</i>						
<i>Bradykinesia Test</i>						
<i>Posturography for Lower Extremity Motor Coordination Test</i>						
<i>Graphimetry</i>						
Imaging						
2 back-to-back 3T MRI scans (T1)	X		X		X	
1 T2 Scan	X		X		X	
1.5T scans (2x) at baseline and one year on subset of 25%	X		X			
Oculomotor Assessment						
Second Order Conditional Conflict Task	X		X		X	
Baseline Saccade Latency and Velocity	X					

Table 13 Detailed assessment plan, cont.

5.6 Study Schedule

The planned study start date is 1st January 2008 at all sites. New staff should be in post by 1st November 2007 with full training for all study site staff at Reisenburg in Germany from the 12th – 15th November 2007. Adverts for new staff should be placed in July 2007, and budgets in place for each site by 31st July 2007. IRB approvals should be in place by mid-September 2007 for each site. Recruitment by site PIs should begin in September 2007 after IRB approval for the first assessments to start in early January 2008. Site PIs should identify potential study subjects now. A detailed Track-HD preparatory phase schedule is available via central coordination.

5.6.1 Ethical/IRB approvals for study sites

All IRB votes will be filed locally for each site. IRB approval at each site is needed for transfer of data to Ulm and LONI and biosamples to Biorep in Milan. These approvals are already in place for transfer of data via EHDN and COHORT and the sites can use this information accordingly. Full detailed patient and control subject information sheets and consent forms (section 6) are incorporated into this protocol for the local site IRB applications. The clinical trial manager, investigator leads for each section and central coordination will answer any queries from the site PIs regarding their IRB applications.

5.6.2 Staff recruitment

New staff should be in post by 1st November 2007 with full training for all study site staff at Reisenburg in Germany from the 12th – 15th November 2007. Adverts for new staff should be placed in July 2007..

5.6.3 Staff training

The site neurologist, study nurse and psychologist will need two months' training. They will train for two months prior to the first subject visit in January 2008, learning the relevant assessments and practising on normal volunteers. The new site neurologist will also observe and rate HD patients in a clinical setting, under supervision. There will be a full 3-day intensive training session in mid-November 2007 in Reisenburg, Germany for motor, oculomotor, cognitive, neuropsychiatric and clinical assessments for all staff. Biosample collection training will be performed locally with the site PIs, clinical trial manager and local lab staff. After training the staff will be assessed for

their competence on each of the cognitive, motor and neuropsychiatric batteries by Julie Stout, Marie-Noelle Witjes-Ane, Ralf Reilmann / Raymund Roos and David Craufurd, respectively.

5.6.4 Subject recruitment

New subjects for assessment from January - June 2008 will be recruited and booked from October 2007 to May 2008. Previous experience has shown that booking subjects approximately 2 months prior to assessment means that subjects have good availability and allows booking of a steady rate of subjects.

5.6.5 Study schedule & milestones

The Track-HD study schedule and milestones are depicted in Figure 22.

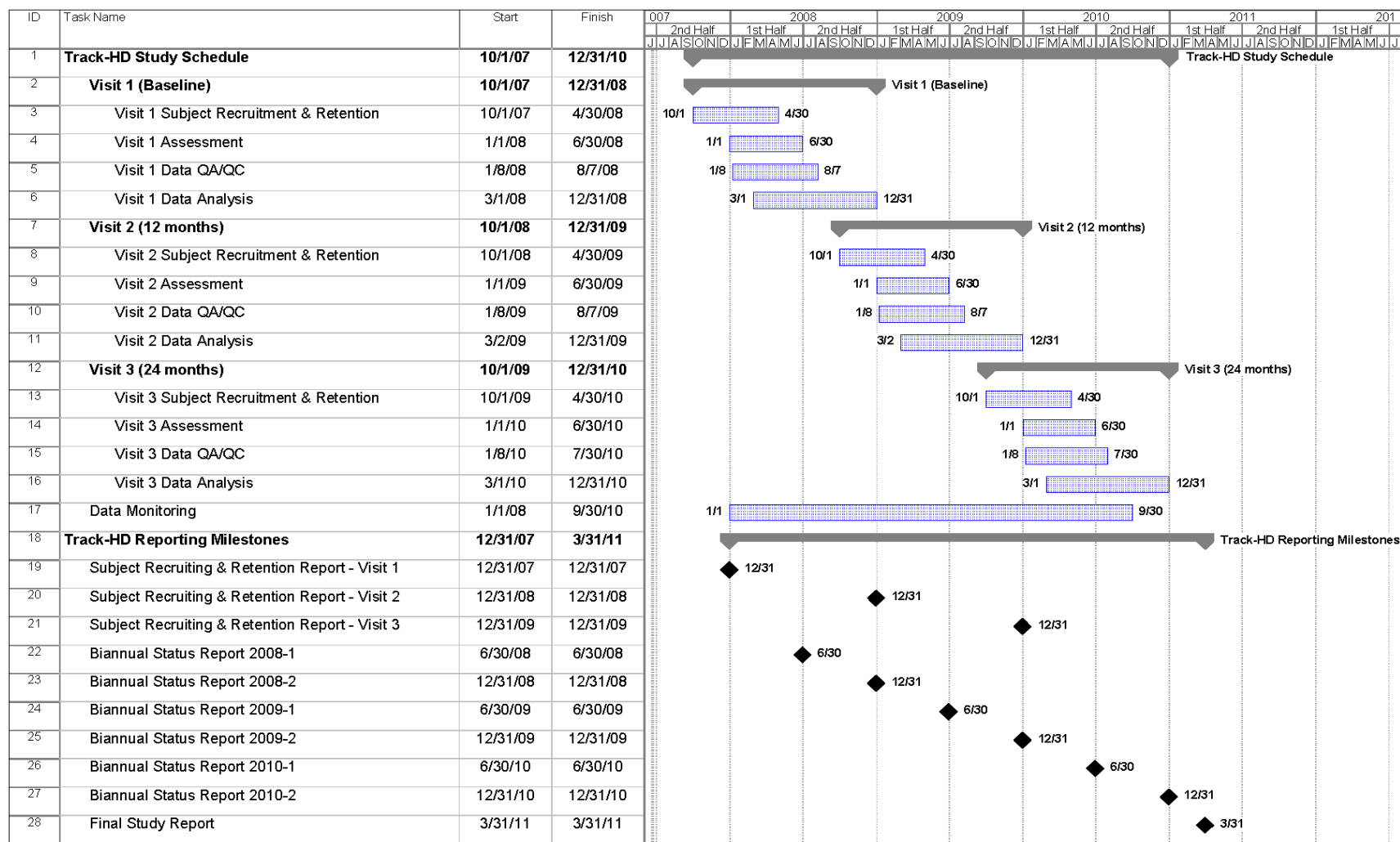


Figure 22 Track-HD study schedule & milestones

5.7 The Track-HD day

Each subject will see a site neurologist, psychologist (P) and study nurse. Ideally, each assessment should take place at the same time of day in each centre. In practice this may not be possible owing to staff and scanner availability. Timings will be recorded as meta-data to allow analysis of the effect of time of day on outcomes. Timings allow for time to move between departments, and short comfort breaks. Subjects are offered more refreshments at the beginning of the clinical and cognitive assessments as well as during those times if necessary. A timetable for a subject visit is shown in Table 14.

Time	Assessment	Details
9:00		Neurologist and study nurse prepares consent form, information sheet, MRI checklist, DPA form P collates necessary testing forms, sets up relevant computer programs Neurologist ensures adequate sample tubes, equipment, questionnaires etc.
10:00	Subject arrival	Subject arrives at centre, greeted by neurologist, nurse and P <ol style="list-style-type: none"> 1. discussion of study, suitability for MRI, subject given copy of information sheet 2. informed consent taken 3. pseudonymisation procedure carried out 4. consent form photocopied and copy given to subject; scanned and electronic copy saved 5. Data Protection Act form signed 6. MRI checklist filled out (first half, contraindications) 7. blood samples taken
10:30	Cognitive Motor	Neurologist, P, and nurse takes subject <ol style="list-style-type: none"> 1. cognitive and quantified motor assessment 2. Neurologist processes biosamples
12:00	Lunch	Taken at subject's leisure to be refunded later
13:00	Clinical Neuropsychiatric Oculomotor	Neurologist and nurse takes subject <ol style="list-style-type: none"> 1. clinical and neuropsychiatric assessment (direct entry to electronic database) 2. self-administered questionnaires 3. oculomotor assessment with saccadometer 4. samples documented
15:00	MRI	Either P or nurse escorts subject to scanner <ol style="list-style-type: none"> 1. MRI checklist completed (second half, removal of all metal objects) 2. subject scanned 3. staff member escorts subject back to the centre
15:30 to 16:00	Subject departure	Nurse, P or neurologist takes leave of subject <ol style="list-style-type: none"> 1. ensures subject is satisfied and all questions answered 2. subject informed when to expect phone call regarding next visit 3. travel expenses and lunch receipts either collected from subject, or subject given SAE to post them back to the centre
16:00		Neurologist or Nurse <ol style="list-style-type: none"> 1. enters remaining data onto electronic database 2. files questionnaires P <ol style="list-style-type: none"> 1. copies data from laptop to central system 2. enters data onto electronic database 3. copies cognitive results for filing in patients' clinical notes P or Neurologist <ol style="list-style-type: none"> 1. transfers scans once available on server 2. brief check for gross problems 3. enters subject scan details in scan log and into electronic database 4. Local check on scan to ensure no clinical abnormalities via local neuroradiologist and then uploads scan to LONI for transfer to Imaging CRO.

Table 14 Track-HD visit timetable

5.8 Study population

5.8.1 Population

The standard cohort for each Track-HD centre will be 30 early disease subjects, 30 premanifest individuals and 30 control subjects.

5.8.2 Inclusion criteria

Written informed consent must be obtained from the subject, who must agree to all the assessments.

- Ability to tolerate MRI and sample donation
- Subjects will be either
 1. **Control subject**
 - a. Partner/spouse of a patient, not at risk of HD (note these subjects will not have CAG repeat testing)
 - b. HD Normal repeat length sibling or HD normal repeat length control volunteer
 2. **Premanifest gene carrier**
 - a. Positive genetic test with CAG repeat length ≥ 40 **and**
 - b. Burden of pathology score $(\text{CAG} - 35.5) \times \text{age} > 250$ **and**
 - c. Absence of diagnostic motor features according to the UHDRS 99
 3. **Early HD**
 - a. Positive genetic test with CAG repeat length ≥ 40 **and**
 - b. Presence of diagnostic motor features according to the UHDRS 99 **and**
 - c. Shoulson and Fahn stage 1 (TFC $> 9-13$) or 2 (TFC ≥ 7) assessed according to UHDRS total functional capacity (TFC ≥ 7) (Shoulson & Fahn, 1979; Shoulson, 1981)

Note: as the PM groups and HD groups will necessarily have different mean ages it is unlikely that the control group will age-match both patient groups. Instead, centres should aim to have a sufficient range of ages in controls to span the ages of the other two groups so that age can be used as a covariate in subsequent analyses.

5.8.3 Exclusion criteria

- Stage 3 (TFC ≤ 6) or greater at time of enrolment
- Less than 18 years of age
- More than 65 years of age
- Major psychiatric disorder at time of enrolment
- Concomitant significant neurological disorder
- Concomitant significant medical illness

- Unsuitability for MRI, e.g. claustrophobia, metal implants
- Unwillingness to donate blood
- History of significant head injury
- Predictable non –compliance by drug and/or alcohol abuse
- Significant hand injuries that preclude either writing or rapid computerized responding
- Participant in Predict-HD
- Currently participating in a clinical drug trial

5.8.4 Recruitment and screening

It is anticipated that patients recruited will be under the care of the HD clinical service at each centre. Prior to being invited to join Track-HD, patients would need to be screened based on already known clinical information. This is especially important in allocating subjects to the premanifest and early disease groups, and in rigorously excluding subjects in clinical stage 3 or beyond.

Manifest subjects with a known HD mutation, but with an unknown CAG repeat length, must have their CAG repeat length tested according to inclusion criterion No 3a prior to enrolment. Premanifest subjects will be recruited based on their disease burden score (see section 5.8.2).

5.9 Personnel

The following staff will be required at each study site:

Staff	Generic duties
Site neurologist	Clinical, neuropsychiatric, motor and oculomotor assessments, take blood, process blood; clinical analysis; check scans locally and transfer scans, electronic data transfer; motor, clinical, genetic and imaging data analysis dependant on research interests
Study nurse	Recruitment and booking of subjects, Processing expenses for subjects, clinical, neuropsychiatric and cognitive assessments, take blood, associated record-keeping; data analysis
Psychology research assistant	Cognitive/quantitative motor assessment; oculomotor assessments, scoring of cognitive tasks; data transfer; cognitive analysis;

These duties are generic and it is anticipated that duties will be shared so two personnel are trained for the assessments in the event of sickness etc. The site PI will cover the site neurologist in the event of sickness.

5.10 Funding

Track-HD is sponsored by the High Q Foundation, a private philanthropic foundation that was established in 2002 with the mission of bringing together academia, industry, governmental agencies, and other funding organizations in the search for Huntington's disease (HD) treatments.

5.11 Data storage and security

In Track-HD, collected data is stored in three different central databases:

- the phenotypical data in CTMS, hosted at the EHDN in Ulm,
- the imaging data in LONI/HDNI, hosted at the UCLA in Los Angeles, and
- the bio samples with resp. data at Biorep in Milan

All data related to study participants will be stored only in pseudonymised manner. Identifying data such as names or contact details will never be stored electronically at any time. Data entered by investigators are only entered via a modern web browser into secure web interfaces (https/SSL). Any data transmission, from the investigator's web browser to one of the systems or among the systems, is done in a secure and encrypted manner (https/SSL).

The participant's pseudonym is created based on unchanging information (date of birth, birth name, place of birth and mother's maiden name) after the inclusion of the study participant. Technically the pseudonym - a nine digit number - is automatically computed by using a secure one-way well-accepted cryptographic algorithm (MD5 or SHA1). The pseudonym creation can only be done by a very limited group of persons (the site staff) and only via the CTMS web system. It is unique, duplicate-free and not reversible. For example the data "Christine Mustermann, Date of Birth: 13 April 1964, Place of Birth: Berlin, Birth name: Maier; Mother's maiden name: Schmidt" produces the pseudonym: 344-259-192.

All sites should have local ethical and data protection approval, particularly for the transfer of pseudonymised data overseas. Since the identifying data is never stored electronically, the investigator will store the original data and the pseudonym in the source documents (patient file) and in the investigator file.

For the protection of each database containing pseudonymised data against unauthorised access several precautions are in place to ensure integrity, confidentiality and security of the database. The servers are managed by full-time system administrators. All network traffic is encrypted via network hubs using SSL/TLS with a key length of 128 or more. Servers have been 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. In addition, other security software runs continuously minimizing other potential attacks. All accounts are password protected.

All phenotypical data will be stored in PostgreSQL, a relational database management system, which resides on a Linux Server running the Linux Operating Environment. The server resides inside a locked computer room that is physically accessible only by the authorized personal. This room is located in the central coordination suite of EHDN at Ulm that is also locked. Different keys are required for both the computer room and the suite. The computer room is temperature controlled. It is equipped with smoke/fire detection sensors. To ensure high system availability the server is equipped with dual power supplies, hot-swappable RAID 5 disk drives, and an APC uninterruptible power supply. Every 12 hours the system is backed up to the a second, mirrored server in a similarly protected environment located at a physically distant (> 50 km) site. All electronic data are fully audit trail enabled so that all changes to the data can be monitored and/or recovered. The CTMS implements a permission-based security methodology that limits access to study data based on the particular study, user ID, and user roles using access control lists (ACL). 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 based on ACLs. Files and directories are carefully set with only the required level of access. Users are required to change password on a regular basis. The password must have a length of at least 8 characters including 2 special ones. Every precaution has been taken to assure that computer confidentiality is maintained.

The secure data capturing of the phenotypical data is summarized in the diagram below (Figure 23).

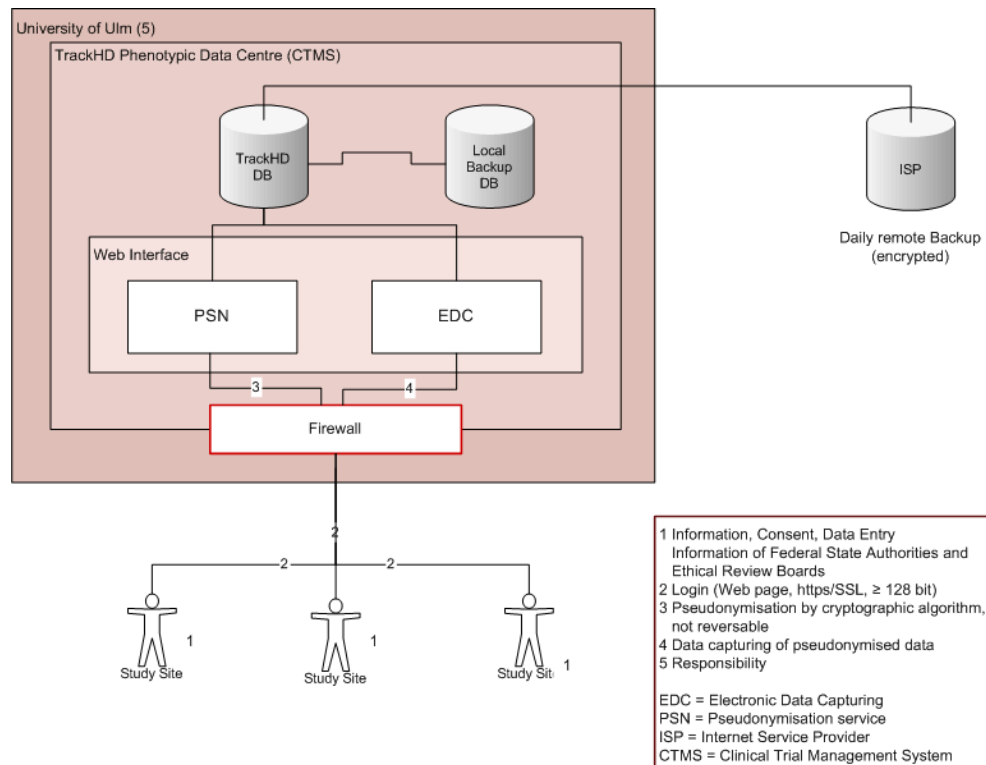


Figure 23 Secure capturing of phenotypical data in CTMS

The workflow for entering data with use to all distributed databases is shown in the diagram below (Figure 24).

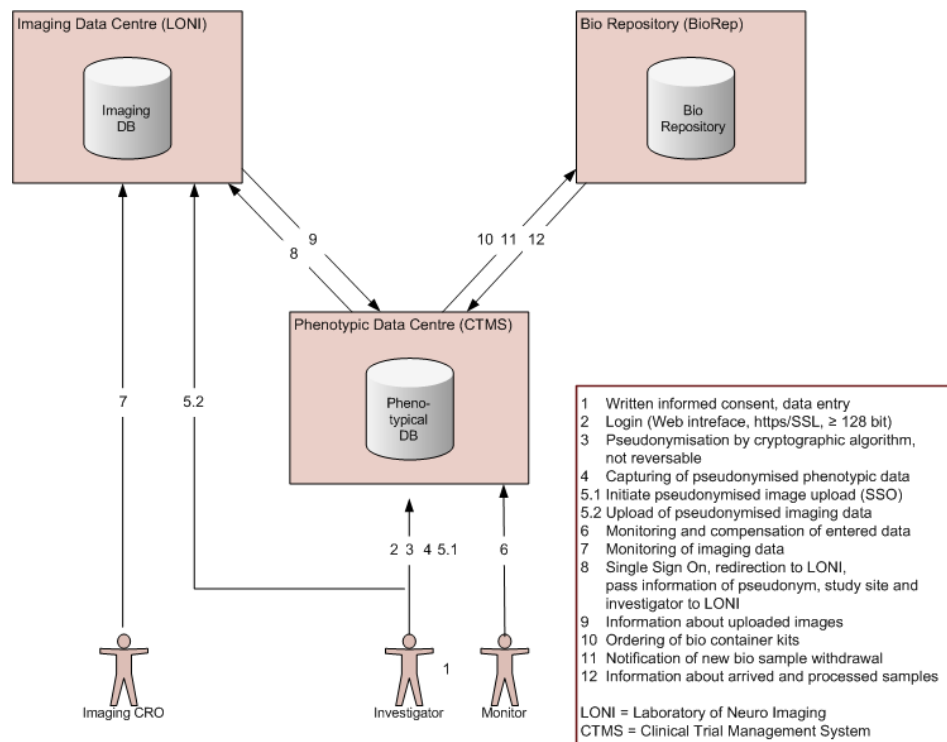


Figure 24 Data entry workflow and databases

5.12 Ethical considerations

5.12.1 IRB and R&D submission

IRB approval for the study and for international data transfer to Ulm and LONI will need to be sought in each country along with local R&D approval. Central coordination will work with site PIs to obtain ethical approval at each site.

The Track-HD protocol will be subject to amendments for clinical tests to be added or removed as new data becomes available during the study's progression. It is imperative at each study site that local IRB amendments for minor protocol alterations can be approved quickly.

5.12.2 Participant costs and expenses

Participants will incur no cost for participation in this study. Participants will receive no payment for participation in this study but will receive full compensation for their travel expenses and the cost of lunch during study visits. Expense refunds will be handled locally by each study centre. Where local ethics committees allow it, control subjects may be offered an honorarium for participating.

5.12.3 Participant risk

Since Track-HD is an observational study, participants do not undergo specific risks by participating; therefore no medical insurance is provided unless the respective national law requires one.

Participants may experience anxiety while completing clinical, cognitive and neuropsychiatric assessments and MRI scans.

In addition, despite best efforts, it is not humanly possible to exclude with 100% certainty a breach of confidentiality by unauthorized people obtaining access to information in medical files and records thus resulting in a loss of confidentiality. All reasonable safeguards to prevent such an occurrence will be undertaken. For instance, all data entered into the electronic database of Track-HD will be stored under a numerical pseudonym rather than name or other identifying data. At all times, only the local site investigators are aware of the identifying data associated with the pseudonym.

All users of the database outside the local study site will work exclusively with pseudonymised data. The database is secured as detailed in section 5.11.

There are additional potential risks associated with phlebotomy. A minor amount of pain inevitable accompanies phlebotomy. The collection of blood specimens may cause bruising at the site where blood is drawn. Fainting or feeling light-headed may occur during or shortly after having blood drawn. If a participant experiences this, the participant will be instructed to lie down immediately to avoid possible injuries. Localized clot formation and infections may occur, but this is very rare. Only experienced staff (site neurologists) will draw blood for this study. In order to ensure the confidentiality of donors contributing to the central repository, Biorep will never receive identifying data along with the biosamples sent for storage. Instead, Biorep will receive the biosamples from study sites with only the pseudonym as identifier.

5.12.4 Potential benefit

Participants will receive no immediate benefit from participation in this study. The only potential benefit is a better understanding of HD and the possibility that the information obtained in this study will lead to potential treatments and to plan future research studies of experimental drugs aimed at slowing disease progression or postponing the onset of HD.

5.12.5 Alternatives to participation

The only alternative to participation in this study is not to participate.

5.12.6 Withdrawal from participation

If a participant does not want to continue, the participant can leave the study at any time. Participants do not have to disclose their reasons for withdrawal of consent. On the participant's request, all information obtained so far will be anonymised (identifying data discarded). Similarly, on the participant's request, all biosamples collected and stored at the central Biorep repository may be destroyed. Participants have to be aware that an 'End of Study form' must be completed by the investigator, detailing the reasons for withdrawal (e.g. marking "patient request").

Participants may be withdrawn from the study for the following reasons:

1. Failure to complete the required study procedures, regardless of reason.
2. The site investigator feels that it is in the best interest of the participant.

5.13 Quality assurance and quality control

5.13.1 Rationale

Quality assurance refers to the procedures put in place to ensure quality, whereas quality control refers to the evaluation of the effectiveness of those procedures. The key distinction is between preparing for quality in the study (quality assurance) and checking for quality of data collected (quality control).

The ultimate aim of Track-HD's QA/QC measures is to ensure that, to the maximum reasonable extent, data that are analysed and published are as true a reflection as possible of the neurobiological state of each subject. Robust measures will be required to ensure a reliable "chain of evidence" from the subject to the point of publication.

As far as possible, QA/QC will be centralised to ensure consistency between all sites and across time. Low tolerance for deviation from protocol and rapid feedback to sites and raters will be essential. The emphasis will be on central QA to ensure consistency. QA will be handled by EHDN-appointed data monitors with site visits 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 needed. Sites will be evaluated at least annually.

5.13.2 Monitoring of database entries

To obtain optimal data quality and reach the highest standards of reliability, Track-HD will be monitored on the basis of the rules of ICH-GCP. After initiation of the respective study site, an independent monitor associated with EHDN will visit the centres in predefined intervals (following the enrolment of the first three subjects – early HD + premanifest + control -, and thereafter every four weeks) to make sure that the centre complies with the Track-HD protocol and the principles of the Declaration of Helsinki.

The first visit (**initiation visit**) will be performed by the clinical trial manager/monitor to make sure that all study site personnel involved with Track-HD are not only familiar with the protocol, the respective SOPs and the EDC methods used within Track-HD but intensively trained in the application of the so-called test batteries. At the initiation visit the Investigator's Study File (a binder with all study related documents, e.g. protocol, IRB approval and insurance certificates, distributed at the training meeting) will be updated and completed by signed CV, the protocol signatures, the financial agreements, copies of the training certificates and the quality certificates of the



equipment employed in the study (Freezer, balance etc) – a short visit at the department of radiology may be necessary).

The quality of phenotypical data collected in Track-HD is ensured through three mechanisms:

- internal plausibility checks provided within the eCRFs
- online monitoring
- regular on-site monitoring visit for source data verification

The plausibility checks of the electronic data capture system will make sure that not only omissions and obviously erroneous entries were identified as such but it will also alert for unusual values and will be able to cross-check the contents of the single CRFs and across visits. Specifically, the in/exclusion criteria are compared with the basic information given e.g. in the patients' history or the report of the genetic laboratory. Incongruence's were highlighted and contradictions will lead to mandatory queries.

The online monitoring provides the feedback for the investigator/data entry personnel within 24 hours after the documentation. Problems, e.g. violations of the inclusion criteria will be discussed and –after consultation with the external experts – waivers will be given, if necessary. The online monitoring also makes sure that, in addition to the automatic reminder system, the time schedule of the visits and tests are followed.

Through the instrument of on-line monitoring the identity of the HD rater and data entry person can be followed assuring that only qualified raters or their designated deputies using with their unique passwords are entering data thus minimising errors in data entry.

The regular onsite monitoring is intended, as defined by ICH-GCP (5.18), to verify

- that the rights and well-being of the subjects are protected
- the reported trial data are accurate, complete and verifiable from source documents and
- the conduct of the trial is in compliance with the currently approved protocol, GCP and the regulatory requirements.

In accordance with the international guidelines, the burden of onsite monitoring in Track-HD is to some extent reduced by the above mentioned e-tools. Nevertheless, on-site source data verification is still necessary.

100% verification of source data will be required for

- Identity (birth date, sex, pseudonym) of the subject
- Informed consent
- In/Exclusion criteria (as defined in 5.8)
- Concomitant medication at the time of inclusion

A sampling of 25% of the video tapes and the time schedule (+/- 6 weeks) as recorded in the files can be considered as sufficient. In Track-HD, the documentation of most test results will be performed electronically; source data are therefore available as part of the data base.

During the onsite monitoring, the monitor has also to verify that the facilities (including the department of radiology), the equipment and the staff are adequate to safely and properly conduct Track-HD by checking

- The freezers used for storing biosamples (temperature logs have to be written)
- Test certificates of the equipment (MRI, Saccadometer)

- The successful transfer of videotapes, MRI images and bio samples to the external experts, the specialized CRO and Biorep

Furthermore, the completeness and up-to-dateness of the investigator's File has to be checked at each visit and the training of new staff has to be ensured.

5.13.3 QA/QC systems for clinical assessment

Quality Assurance

UHDRS motor assessment is an important core assessment but also a major potential source of experimental variability.

All clinical raters will be trained and assessed in UHDRS motor assessment according to the standards of the EHDN Motor working group including annually repeated video motor ratings on which a permanent record is kept (see video rating in Track-HD SOP documents).

Data will be checked locally for missing or erroneous data. Central automated checking will highlight data anomalies which can be raised with the study site within 24 hours.

Quality Control

All motor assessments will be digitally video recorded (see video recording in Track-HD SOP documents) for reference and a subset securely transmitted to a motor QC panel for independent verification of results and feedback regarding technique. This will be applied to a subset of 25% randomly chosen. Dr Ralf Reilmann has agreed on behalf of the EHDN Motor working group to convene the motor QC panel.

In addition, we recommend periodic direct observation of the clinical assessment (including the demographic and medical interview) by QC personnel appointed by central coordination, to ensure that the clinical battery is being administered by each rater in accordance with the SOP.

5.13.4 QA/QC systems for functional and QoL assessment

Quality Assurance

The QOLI and SF 36 will be mailed with detailed written instructions to the subject in due / appropriate time prior to their clinic assessment date. The subject version will be mailed with the HADS, SIS and the SF-36. These instructions will emphasize the need to complete the questionnaire without outside help. A phone number will be provided if an individual has a question. A reminder phone call will be made the day prior to the appointment. If the subject fails to bring the completed QOLI and SF36 to the clinic on the assessment date and the subject is unable to complete these forms at the end of the assessment day, an additional copy will be provided to the subject with a self-addressed postage paid envelope. The subject will be encouraged to complete and mail the missing rating forms the next day. A follow-up reminder call will be made the day after the clinic visit. If the completed rating forms are not received within 8 business days, an additional reminder call will be placed. Completed forms will be centrally checked for scoring and quality control.

Training, certification, and re-certification of UHDRS TFC examiners – Examiners will be trained on TFC as part of preparation for the study.

Quality Control

Data will be monitored centrally for completeness and range of values. Any anomalies found in the data will be followed up by further training at the sites.

5.13.5 QA/QC systems for neuropsychiatric assessment

Quality Assurance

Training, certification, and re-certification of examiners for the PBA – A standard training package for English speaking behavioural raters of the PBA has been developed. To assist in training, Dr. Craufurd has videotaped the administration of the PBA with 9 HD patients. After a brief introductory talk, neuropsychiatric raters spend 4 hours viewing, scoring and discussing videotaped interviews, then 3 hours doing ‘live’ interviews with real patients in small groups. In groups of four (3 inexperienced raters plus an experienced rater), raters take turns interviewing patient volunteers. To date, two people from the Netherlands have been trained; Erik van Duijn, who is a psychiatrist, and Renier Timman, a psychologist. Dr. van Duijn has helped run international training workshops, and will be responsible for training additional Dutch Euro-HD neuropsychiatric raters. Reliability and validity testing are in progress. Data collected from training workshops will provide an estimate of inter-rater reliability in novice examiners. Preliminary evidence suggests that with appropriate training, high levels of agreement are attainable.

Three French raters have also been trained Catherine Bourdet (a psychiatrist who was part of the group that helped us develop scoring guidelines for the original long PBA) and Marie-Françoise Boissé (psychologist) from Créteil, and Marie-Agathe Zimmerman (another psychologist) from Strasbourg. They are currently preparing for a French language training workshop.

BDI-II. The BDI-II will be given to the participant to fill out immediately after completion of the PBA-S. No special examiner training is required.

HADS, SIS and FrSBe data acquisition – The HADS, SIS and FrSBe will be mailed with detailed written instructions to the subject 10 days prior to their clinic assessment date. The companion version of the FrSBe, SIS and Irritability Scale for Huntington’s disease will be mailed under separate cover in due/appropriate time prior to the clinic assessment date to provide sufficient time for diary ratings. Instructions will emphasize the need to complete the questionnaire without outside help. A phone number will be provided if an individual has a question. A reminder phone call will be made the day prior to the appointment. If the subject or companion fails to bring the completed forms to the clinic on the assessment date, an additional copy will be provided and the subject will be asked to complete the forms following the PBA interview or at the end of the assessment day. Completed rating forms will be forwarded to Manchester for final scoring and quality control.

Translation of the PBA – The Dutch version has been translated and Erik van Duijn has already been working on the validation of the long version of the PBA in Dutch translation. Work has also started on the French translation, which is being done by the three trained French psychiatrists / psychologists.

To validate the translated versions of the PBA, 50 - 60 real interviews will be conducted in each language from the Euro-HD Registry clinics, and then second-rated by another trained rater, either by sitting in on the interview or by viewing a recording of the interview. Thirdly, if funding is available, a small number of interviews will be translated into the other major languages and sub-titled so they can be independently scored to check inter-rater reliability across linguistic and cultural barriers – 3 interviews, each rated by 20 people, would provide the 60 comparisons required to do this.

Translation of the BDI-II, HADS, FrSBe, and ISHD will be undertaken according to the standard procedures employed in Track-HD.

Quality Control

Data Quality will be monitored by David Craufurd and colleagues in Manchester by reviewing data from at least a sample of 2 participants from each site annually. Specifically, this data review will include an inspection of the data for completeness, inspection of frequency distributions and range across sites to check for potential differences in administration. Any anomalies found in the data will be followed up by further training at the sites.

5.13.6 QA/QC systems for biosample collection

Quality Assurance

All personnel will be trained and observed in collecting and processing blood from volunteer subjects to ensure protocol compliance.

All consumables (except for dry ice) will be provided by Biorep to ensure consistency between sites and minimise potential processing error. Tubes will be labelled and colour-coded to prevent confusion. On-site QC includes a visual check for plasma quality to prevent the inclusion of haemolysed samples.

To prevent sample misidentification, patient samples will be processed immediately on-site one at a time and stored in labelled, bar-coded tubes with immediate recording of identifying information. Biorep has in place robust QC measures to ensure continuing integrity of samples and metadata.

Quality Control

Biorep will analyse incoming samples for quality. Plasma will be analysed for haemoglobin contamination due to haemolysis using a HemoCue plasma Haemoglobin analyser. Creatine phosphokinase, lactate dehydrogenase and C-reactive protein levels will be measured spectrophotometrically as markers of plasma protein integrity. Periodically samples will also be assessed by Prof Elaine Holmes (Imperial College) using NMR analysis.

5.13.7 QA/QC systems for cognitive assessment

Quality Assurance

Training – Cognitive Examiners must be trained at a face to face training session and certified by an approved cognitive trainer prior to running any participants. Prior to face to face training, the trainee should review the operating procedures manual.

During the face to face training, the following occurs:

- Trainer instructs trainees on optimizing patient test performance
- Trainer instructs trainees on importance of and methods for standardized administration
- Trainer orients trainees to the test battery
- Trainer demonstrates test battery administration
- Trainees practice full test battery administration on each other with informal feedback from trainer
- Trainee administers full test battery to trainer
- Trainer provides written feedback to trainee and either
 - Certifies the trainee to test participants with the caveat that the initial administration must be videotaped and sent in for evaluation, OR



- Requires trainee to do additional work, including
 - practice at the home site to address shortcomings highlighted in the written training session feedback
 - video recording of a practice administration of the test battery
 - Certification based on the trainer's rating of the videotaped practice administration

This training and certification process is executed each time the test battery is changed in any way that alters the test battery administration. In addition to initial certification, each cognitive examiner must submit a videotape of at least one test administration per year. This tape is reviewed by a cognitive trainer and written feedback is provided to the examiner. In some cases, corrective action will be required and the trainer may request a second videotape of a battery administration that demonstrates the cognitive examiner has addressed the trainer's concerns.

Equipment - Standard operating procedures require calibration all relevant hardware before each administration. The touch surface of the tablet PC needs to be calibrated to increase precision of spatial measurements. Document scanners require setup to be done consistently to maintain quality of scanning from site to site. For audio recordings, the hardware and the software need to be setup properly to ensure a useful recording in every circumstance.

Quality Control

All paper/pencil tasks will be scored by the examiner at the home site and then rescored by a certified scorer. Discrepancies will require a third scoring. A cognitive trainer will provide feedback to the examiners who produce score that are consistently discrepant from those of the secondary and tertiary scorers.

Electronic Data Collection Quality Control – Data generated by electronic means must be collected, recorded and reported, as consistently, accurately and precisely as possible.

- Collection refers to the administration of the tasks by cognitive examiners.
 - Collection must be done in a consistent and reliable way such that the data are not affected by individualized administration practices.
 - Cognitive examiners will be trained on proper administration of the tasks to reduce collection errors as much as possible.
- Recording refers to the dependent variables of the computerized task, such as response time, or inter-tap-interval variance.
 - As the tasks are written, each program undergoes a strict QA process to verify that the program is measuring what it claims to measure within the required specifications and this reduces recording errors. All data measured by the tasks must be as accurate and precise as possible for all hardware.
- Reporting refers to the association of data with the correct administration in the database.
 - Each participant number from each site for each visit must be correctly linked to the proper and complete set of administration data for the tasks. Time and date stamps are taken for each task administration, and additionally participant number, site and visit numbers are all recorded for each battery administration. This information, along with notes about the administration from the cognitive examiner, are used to link the electronically collected data to the official list of administrations. This reduces reporting errors.

5.13.8 QA/QC systems for quantified motor assessment

Quality Assurance

Validation of the hardware and software – All equipment will be assembled and tested at the laboratory of Dr. Ralf Reilmann in Muenster and shipped to the study sites. After the equipment is installed at individual sites, 1-2 mock participants will be assessed using the complete protocol. These data will then be sent to Dr. Reilmann for inspection to ensure that the equipment has been correctly installed at the sites, is working, and is producing usable and accurate data.

Calibration of equipment

The force transducer, force-plate, and Polhemus 3D-position-sensor used for the assessments are industrial standard pre-calibrated systems at factory delivery and do not require recalibration. They are used in robotics in industrial processing and calibration is assured by electronic circuits including adjustments for temperature

Training, certification, and re-certification of examiners

All examiners must be trained in a face-to-face setting by a certified trainer. As part of the training, the trainer will observe the examiner administering the tasks, provide written feedback to the examiner regarding the administration of each of the tasks, and, when the examiner is considered to have the skills for standard task administration, the trainer will add the examiner to the list of certified Track-HD quantitative motor examiners. Re-certification is required on an annual basis and can be accomplished either in person or by videotapes available via the EHDN motor training website (again, reviewed by a certified trainer for approval of recertification). In addition, videotaped sample assessments of all paradigms used will be made available on the EHDN website.

Quality Control

Data Quality will be monitored by Dr. Reilmann and colleagues in Muenster by conducting intensive review of the data from 1-2 mock participants at each site before the start of the study, and then by reviewing data from participants from all sites within four weeks of delivery. Specifically, this data review will include an inspection of the data for completeness, and range to check for range violations. Any anomalies found in the data will be followed up by either further training at the sites or checking and repair of the equipment as necessary.

5.13.9 QA/QC systems for imaging assessment

Quality Assurance

HDNI and the Imaging CRO will put in place QA procedures to ensure that scans obtained at different times in different centres using different hardware/software combinations are as comparable as possible. This will include standardisation of scanning protocols and inter-scanner comparisons using phantoms or human volunteers. The Image Acquisition preparatory phase work for Track-HD is being led by Professor Nick Fox and IXICO Ltd.

Quality Control

The local site PI is responsible for ensuring clinical assessment of the scans by a local radiologist within five working days of the scan and will be responsible for clinical follow-up if any abnormalities detected.

Imaging QC and feedback to sites will ultimately be carried out centrally by the Imaging CRO. This is detailed in the Imaging Track-HD SOP document.

5.13.10 QA/QC systems for oculomotor assessment

Quality Assurance

All testing sites will be provided with a Saccadometer and experimenters will be trained and assessed in the administration of the oculomotor test battery. During the first month of testing, January 2008, a member of Professor Christopher Kennard's oculomotor team will make a personal visit to each of the testing clinics in London, Leiden and Paris. The purpose will be to observe how the oculomotor test battery is administered. Particular attention will be paid to:

1. The suitability of the testing environment and the handling of the saccadometer,
2. The manner in which participant instructions are given, and their comprehension,
3. The timing of the test, that it is completed within 30 minutes, and
4. That the data collected is of the highest quality and is being uploaded correctly.

The testing clinic in Vancouver will be observed by video recording. The major elements of the oculomotor test battery are easily visible at a distance and the quality of the data can be assessed via the CTMS. A physical trip to Vancouver will be undertaken if one of the following occur; either significant problems are revealed in the video recordings, or if the three European clinics experience systematic problems.

Quality Control

Once the oculomotor test battery is running as planned, QC becomes focussed on data management. The primary QC will be weekly checks via the CTMS to ensure that the data is being stored correctly. This will be assessed in the following ways:

1. The number of data files added to the database per week will be compared with the expected amount.
2. Data files for that week will be downloaded and checked to ensure that they can be opened with the program LatencyMeter (Ober Consulting), that the Clinic, Experimenter and Subject IDs are all entered correctly, and that the data itself fits the expected profile.

5.14 General statistical principles for Track-HD

5.14.1 Underlying assumptions: relationship between Track-HD study design & goals

To quote section 4.8:

The primary aim of the study is to provide essential methodological advances needed for optimizing neuroprotective clinical trials in premanifest and early HD. Specifically, Track-HD will be used to examine the sensitivity of individual and combined clinical and biological outcome measures for tracking progression. The secondary aim is to determine what combination of measures is the most sensitive for detecting change over the natural course of premanifest and early HD, with a view to validating these as potential outcome measures for use in future therapeutic trials.

A number of assumptions are implicit in the marriage of this objective to the study design of Track-HD. We here attempt to make these assumptions explicit with the goal of clearly linking the planned data analysis to the study objective.

Longitudinal changes in the outcome measures (candidate markers) are the primary objective of study.

For the CAG-expanded groups, regardless of whether diagnosed at the beginning of the study, naturalistic observation of longitudinal change mimics the course expected of future clinical trial participants receiving either a placebo or a completely ineffective treatment. This assumption seems logical such that it can be made with some confidence. (However, it does not allow for the possibility of true placebo effects in future trials.)

For the non-expanded control group, longitudinal change mimics the course that would be expected in a completely effective treatment of HD under the additional assumption that the characteristic in question is a valid surrogate outcome. This assumption is clearly less certain. For example, it is conceivable that a completely effective treatment could either lead to reversal of previous HD-induced change or fail to immediately arrest the “momentum” built into longitudinal changes that are occurring at the time effective treatment is introduced. Nonetheless, in general it seems difficult to preferentially choose and quantify either of these alternatives.

Change that is observed in the control group will reflect a number of other phenomena associated with longitudinal observation: (a) imperfect measurement reliability (b) short-term within-subject fluctuation in the true phenomenon being measured—which, along with (a) leads to regression towards the mean—(c) background long-term causative effects such as aging, and (d) practice effects. These phenomena are also assumed present, and in a similar degree, in the CAG-expanded groups, along with the potential longitudinal effect of evolving HD.

Given the prior assumptions, the differences in longitudinal marker change between the CAG-expanded groups and the control group are estimates of the maximum possible surrogate treatment effect achievable via that marker in a clinical trial. Since hypothesized treatment effects will typically be considerably less than 100%, these longitudinal differences will need to be notable if the marker is to pass this criterion for candidate surrogacy.

None of the above is meant to distract from the other considerable hurdles that a marker must overcome in order to reach surrogate-outcome status.

Even markers that do not qualify as surrogate outcomes can be quite valuable as risk stratifiers. It can be shown that various strategies related to stratification in recruitment and/or analysis lead to substantial improvement in the power of clinical trials. Thus we do not underestimate the importance of a secondary goal of the study, cross-sectional comparison of groups on the basis of candidate markers.

5.14.2 General principles of statistical analysis

We will strive to always distinguish between a priori and post hoc hypotheses, with a priori hypotheses defined as comprehensively as possible before data analysis begins. An honest distinction is critical to true progress and optimal allocation of future resources in HD research, since the nominal statistical significance for a post-hoc hypothesis, suggested only by preliminary exploration of the data, is typically inflated in ways that are often impossible to quantify (Good & Hardin, 2006).

We will rely on mixed effect linear models to assess most longitudinal change (Verbeke & Molenberghs, 2000; Littell et al., 2006). Fixed effects will typically include group (diagnosed, premanifest, or control), age, gender, time-since-first-measurement (“time”, which will be 0 at baseline), and interactions between group and time. Substantial interactions between group and time will usually be the main parameters of interest. Other fixed covariates will be determined by anticipated confounders for the specific outcomes. For example, most psychometric tests require adjustment for years of education. Subjects will typically have 3 measurements over 2 years. Our primary hypotheses will treat time as a linear effect unless there is a compelling a priori reason to use 2 degrees of freedom in estimating separate 1 and 2-year effects. Secondary analyses will typically explore whether longitudinal change is

related to estimated prognosis within the premanifest group (based on CAG and age) or disease severity within the diagnosed group (based on motor score, functional capacity, or baseline values of a candidate indicator). Random effects will always include a within-subject term. Our sample size will be such that we will generally model unstructured within-subject covariance over the three visits. Other candidate random effects will include variance components for study site and examiner, as appropriate.

Certain longitudinal outcomes will not be amendable to the methods described above in 2. Categorical outcomes or counts will instead be modelled using mixed generalized linear models (e.g. logistic, Poisson), with other considerations identical to those above (Agresti, 2002; Littell et al., 2006). Conversions of status (i.e., diagnosis) will be analyzed by survival analysis. Multivariate-outcome imaging data present special longitudinal challenges. Changes over a single time interval can usually be approached using methods designed primarily for cross-sectional analysis. (The one set of changes is the single “cross-sectional” measurement.) In other instances, the multivariate data are reducible to one or a few summary statistics that can be handled by standard longitudinal methods. These limited generalizations notwithstanding, analysis plans for the imaging component will be described separately below.

Cross-sectional analyses will typically be by linear model with the fixed effects described in 2 above as the predictor variables. Scientific interest will generally focus on group effects between controls, premanifest, and diagnosed, with contrasts involving controls of greatest interest.

Longitudinal studies inevitably entail loss to follow-up. We will monitor drop-out rates and, prior to final analyses, we will investigate whether probability of drop out is predictable on the basis of information known about the subjects, including research data acquired at previous visits. If there is notable drop-out, it appears unpredictable (“completely at random” in statistical parlance), and there is no basis for suspecting that it is related to outcomes of interest, then we will proceed with the previously described methods without modification. For our analyses using mixed modelling theory, we will proceed if the data appears predictable based on known data regarding the subjects (“missing at random” but not “missing completely at random”), as these methods handle such missing data appropriately. In other analyses with substantial, plausibly “missing-at-random” data, we will employ multiple imputation methods to assess the effect of such drop-out on our analyses. If there is substantial drop-out and strong reason to think that it is not missing at random, then our analyses will be subject to sensitivity analyses across a range of assumptions regarding the relationship between drop-out and outcomes. All principles and procedures mentioned in this paragraph are reviewed in greater detail by Verbeke and Molenberghs (2000) and Molenberghs and Kenward (2007).

5.15 Data analysis

5.15.1 Key questions for Track-HD across assessment domains

1. Predict-HD has demonstrated detectable change in a variety of measures over a period of 2 years. Because the goal is to develop assessment strategies to detect disease modifying treatment effects, demonstration of disease progression over a shorter time period is needed. Therefore a key question for Track-HD is “What individual or composite measure within each assessment domain shows the greatest change (largest effect sizes) over a one year time period?”
2. For those measures with the largest longitudinal effect sizes, what sample sizes are needed over what intervals to detect disease modifying effects?

3. How do domain specific effect sizes per interval compare and how might data be combined across domains to reduce redundancy, enhance the variance for which we can account, and ultimately increase efficiency of clinical trials?

Analytical comments:

- a) Within the bounds set by recruitment guidelines, subjects are, in theory, entering into Track-HD at arbitrary points in the HD development trajectory. Therefore, the annual slope estimated by modelling longitudinal change over two years provides an estimate, statistical significance, and implicit power information regarding rates of one year change. However, it must be recognized that repeated measurement effects such as learning effects may have an impact on some of the measurements. This is known to be an issue for many cognitive measures. (See 5.15.7 below.) Therefore, we will also conduct secondary analyses looking specifically at observed effects over only the first year in order to test the consistency of inference from two year observations. Further, if new measurements are introduced later in the study, we may only have one year of data one these from most subjects. Longitudinal analysis will proceed along guidelines outlined in 5.14 even in this case, with the results obviously directly applicable to the one-year hypothesis.
- b) The general strategy outlined in 5.14 will provide estimates and standard errors of longitudinal change, variance, and within-subject covariance for each outcome. These will be readily combinable with hypothesized treatment effects to estimate sample size/durations, with confidence intervals, for future clinical trials. The approach is the same that Langbehn used (section 5.16.2) to advise on sample size for Track-HD.
- c) The relevant effect sizes for outcome comparisons are defined by change per unit of time divided by the mean within-subject residual standard deviations. This information is a product of the general analytic approach described above. The combination of longitudinal outcomes is subject to strong caveats discussed above in 5.14. Bearing these limitations in mind, we will attempt to maximize longitudinal variance explained via principal component analysis of the set of standardized change scores, adjusted for background covariates, and via canonical correlation analysis of these change scores and separate, well-validated prognostic variables (at a minimum, with CAG-age estimated probability of onset).

5.15.2 Secondary questions for Track-HD

1. What is the earliest point during the premanifest disease process that longitudinal effect sizes for any measure become sufficient to useful in a clinical trial?
2. What are the key demographic and clinical variables, which must be taken into account to maximize measure sensitivity, such as age, education level, IQ, sex, etc.?

Analytical comments:

- a) With the planned follow-up time, few actual conversions to a clinical HD diagnosis are anticipated. Further, it will be impossible to know the true time from diagnosis for those who are greater than two years away. Therefore, the best that can be done in addressing this question is examination of longitudinal changes versus separate, already validated prognostic indicators. We will test relationships between longitudinal change and CAG-age based estimated time until diagnosis and striatal volumes.

- b) As discussed in 5.14, potential demographic and clinical confounders, as identified by the investigators, will be controlled as statistical covariates in the longitudinal and other analytical models.

5.15.3 Functional and QoL data analysis

Data will include a variety of summary scores from ratings scales (clinician rated and self-report).

Ancillary questions and analysis plans specific to functional and QOL assessments:

1. What are the relationships between functional and quality of life assessments and other phenotypic and imaging measures described above?
2. These measurements are of special interest, as they attempt to measure a quality that has some face validity as an outcome for clinical trials. We will analyze longitudinal change in functional assessments as a function of group status and validated prognostic indicators using the methods outlined in 5.14 and 5.15.1. If measurable changes can be shown for these measures, potential associations with other Track-HD outcomes will be investigated using adjusted correlation analysis and canonical correlation methods similar to those discussed above in 5.15.1.d.

5.15.4 Neuropsychiatric data analysis

Data will include summary values from individual neuropsychiatric ratings scales (self report and clinician rated).

Ancillary questions and analysis plans specific to neuropsychiatric data

1. Are individual or composite neuropsychiatric measures best used as covariates or outcome measures in clinical trials?
2. What neuropsychiatric characteristics alter the relationships between estimated proximity to onset and variables from other domains, i.e., cognitive, quantitative motor?
3. Longitudinal analyses of neuropsychiatric variables as outcomes will be by principles set out in 5.14 and 5.15.1. Since (potentially fluctuating) psychiatric status may confound other measurements, especially certain aspects of cognitive and physical examination, selected neuropsychiatric measures such as depression scores and others specified by the investigators will be tested as potential confounders using methods addressed in 5.14 and 5.15.2.

5.15.5 Biomarkers in plasma data analysis

Proteomic, neuroinflammatory, transcriptomic, and metabolic markers identified from our current ongoing biomarker research initiatives will be further validated using the Track-HD plasma and RNA samples. Specific *a priori* candidates will be analyzed using the general longitudinal approach described in 5.14. Any additional screening for new candidate markers will be subject to multiple comparison corrections (e.g. false discovery rate) in assessing the probable statistical and scientific significance of the results. Changes in each of the laboratory biomarkers identified will be correlated with the clinical and imaging phenotypic data using multi-variate assessments.

5.15.6 Genetic modifier data analysis studies

In collaboration with the EHDN Registry, the EHDN Genetic Modifiers working group, the HSG COHORT study and Professor James Gusella (Harvard) we will use lymphoblastoid cell line DNA together with clinical and family history data for

identification of genetic modifiers of age of onset and the different clinical phenotypic presentations of HD. Identification of genes that modify the pathogenic process in HD offers a direct route to validate targets for development of HD experimental therapeutics. Track-HD will provide a wide range of HD-associated phenotypes by which to identify modifier genes. Initially, the phenotypes available will be derived from clinical assessments (UHDRS), but the collection of biological samples will also permit the study of additional phenotypes at the levels of RNA, protein, metabolites and cultured cells. The combination of phenotypic and genotypic information will permit analysis of relationships between individual polymorphisms and genes and the effect they have on modifying the phenotypic presentation, rate of progression and response to treatment of HD using genetic linkage and genome-wide association strategies.

5.15.7 Cognitive data analysis

Data will include summary variables from individual cognitive tasks, generally indicating either response times and number of correct items. In addition, we will use factor analyses (or other means of creating composite scores from multiple variables) and examine factor scores as dependent variables.

Ancillary questions and analysis plans specific to cognitive data

1. What are the key demographic and clinical variables, and the practice effects, that must be taken into account to maximize the sensitivity of the cognitive data, such as age, education level, IQ, sex, etc.?
2. For individual tests, how do practice effects need to be taken into account to maximize utility in the context of a clinical trial?
3. Longitudinal analyses will be by principles set out in 5.14 and 5.15.1. Potential confounding is addressed in 5.15.2. The use of controls to study practice effects is addressed above in 5.14.

5.15.8 Quantitative motor data analysis

Data will include summary variables from individual motor tasks, generally indicating either response times and number of correct items. In addition, we will use factor analyses (or other means of creating composite scores from multiple variables) and examine factor scores as dependent variables.

Ancillary questions and analysis plans specific to quantitative motor analysis:

1. What are the key demographic and clinical variables, and the practice effects, that must be taken into account to maximize the sensitivity of the quantified motor data, such as age, education level, IQ, sex, etc.?
2. For individual tests, how do practice effects need to be taken into account to maximize utility in the context of a clinical trial?
3. Longitudinal analyses will be by principles set out in 5.14 and 5.15.1. Potential confounding is addressed in 5.15.2. The use of controls to study practice effects is addressed above in 5.14.

5.15.9 Imaging data analysis

Measures will include: VBM (Frackowiak and Ashburner); BSI-derived atrophy rates for whole brain, caudate, putamen (Fox); volumes from automated segmentation of striatal structures (Johnson); cortical thickness (Rosas). Cross-comparisons between each of these image-analysis methods will be undertaken. Other measures will include correlation between 3T and 1.5T measures.

Each imaging measure will be assessed individually by determining the sample sizes needed in order to detect (with sufficient power) a disease-modifying effect of the magnitudes listed above. This will allow imaging measures to be compared, both with each other and with the other clinical phenotypic parameters described below. Secondary analyses will look at the associations between imaging measures and other measures (clinical assessments, CAG length, CAG-age prognosis, cognitive profile, neuropsychiatric scores, oculomotor measures, motor assessment, functional measures, wet biomarker profiling etc.). Note that, in addition to the usual CAG-age prognosis, CAG length is of separate interest for imaging and other biological markers, as modification of the huntingtin protein's biological effect is a function of CAG length.

Finally (as with all measures) models will be fitted to see whether a combination of measures (either within a modality or across modalities) can reduce the sample sizes needed to detect a disease-modifying effect.

5.15.10 Oculomotor data analysis

The oculomotor data will be preprocessed from the raw data by the Kennard group using the LATER plot method (Carpenter et al., 2000) to create a quantitative description of the saccade latency distribution. From the LATER plot we are interested in three elements:

1. The median latency
2. The slope of the major and minor components of the latency distribution
3. The relative proportions of each component

These data will be used in the following key comparisons:

1. Saccades in the reflexive task vs prosaccades in the conflict task
2. Anti-saccades vs pro-saccades, including the error rate
3. Latency differences as subject switches between rules in the conflict task

These three comparisons may be combined to create a detailed analysis of an individual's eye movement profile. This analysis will be used to address the main question which is:

“Can saccade characteristics be used as early indicator of cognitive and motor deficit progression in premanifest patients?”

Statistical analyses will be based on methods and principles generally outlined in 5.14 and 5.15.1 Post hoc approaches to combining the 3 oculomotor measures will follow guidelines discussed in 5.15.2.

5.16 Sample size considerations

5.16.1 General comments

While sample size estimates can be calculated from the literature for individual measures for desired power, significance and effect sizes, this exercise can only be performed over the interval originally studied, for the individual measure under investigation. Measurement intervals cannot be calculated for other intervals. Moreover, the aim of Track-HD is to generate multivariate, multimodal data with high temporal resolution. Until the desired measures have been measured simultaneously over the shortest desired interval (this is not yet known), calculations cannot be performed to determine the required sample size for reliably identifying the optimum multimodal battery of measures in premanifest and early HD, or calculating the cohort size required for such a battery to be able to detect the effect of a disease modifying intervention.

Data from existing, single-modality studies will only tell us subject numbers for each measure individually, but will give no indication of subject numbers required to evaluate multimodal combinations of biomarkers.

5.16.2 Sample size estimates from Predict-HD data

Using data from premanifest subjects in the Predict-HD study, Doug Langbehn has produced a number of models for the ability of Track-HD to generate sample size estimates for disease-modifying trials. These range from “very optimistic” to “pessimistic” based on the power of the measurements to detect change but do not take into account the possible additional power of combining several measurements. We recommend adopting the “guarded optimistic” model, which suggests that between 4 and 8 centres will be required. Currently 4 sites of 90 subjects each are being instigated.

5.17 Modification of the protocol

Any modification of the protocol which may have an impact on the conduct of the study, including study objectives, study design, participant population, study procedures or significant administrative aspects, will require a formal amendment to the protocol. The organising group and the 4 local IRBs will agree upon such amendments during the course of the study.

5.18 Administrative responsibilities

The investigator must follow national guidelines for good clinical practice and is responsible for the safety and the medical care of the participant.

A contract will be issued to regulate the obligations and rights of the investigator and the responsibilities of the Track-HD trial coordination including the sponsors; the contract will be signed between authorised representatives of the respective institutions with which the investigators are affiliated and Track-HD trial coordination.

The Steering committee of Track-HD is responsible for overseeing the monitoring and data quality control procedures. EHDN Central Coordination is responsible for the execution of monitoring according to the principles of Good Clinical Practice and for supplying trained personnel for this purpose. HDNI is similarly responsible for imaging data and metadata.

The Steering committee of Track-HD is responsible for promoting inclusion into Track-HD and for developing the protocol of the Track-HD study.

5.19 Publications and data access

5.19.1 Data analysis by Track-HD investigators

The Track-HD outcome data will be authored and published by the Track-HD investigators, and all publications will be finally ratified by the Steering committee and biostatisticians.

5.19.2 Data access and data sharing

Sharing data and other biomedical research resources (including biological specimens) reinforces open scientific inquiry, encourages diversity of analysis and opinion, promotes new research, makes possible the testing of new or alternative hypotheses and methods of analysis, supports studies on data collection methods and measurement, facilitates the education of new scientists, enables the exploration of topics not envisioned by the initial investigators, and permits the creation of new datasets when data from multiple sources are combined.

There will be an Access to Data Policy that follows the guidelines of the EHDN (see full details at <https://www.euro-hd.net/html/network/project/constitution/docs>). Individual access to the clinical database and to biosamples will be regulated in

accordance with the policies of EHDN. The members of the EHDN Scientific Review Committee will serve as the Track-HD SRB. Researchers interested in obtaining data for further analysis will submit brief outlines of their HD related research project to the Track-HD Scientific Review Board (SRB). The SRB will assess whether the proposed project falls within the subject area to which participants gave their informed consent (i.e. studies establish and validate biological markers for HD) and whether the proposal is ethically and scientifically sound. Once a project is approved by the SRB, the proposer must confirm in writing to comply with the data access and publication policy. Researchers conducting an approved project will then be granted access to explore a recoded excerpt of the clinical database for selection of appropriate samples based on phenotypic characteristics as well as Biorep's database to explore availability of samples.

The database to which the researchers conducting an approved project is granted access is recoded in order to (1) control for double publication of the same data sets and (2) avoid researchers recognising data sets as their own contribution. In parallel and prior to the release of samples, confirmation will be sought from the respective leading national Ethical Review Board that no objections are raised against the assessment by the SRB that the proposed research project falls within the subject area to which participants gave their informed consent.

The following common language for Clinical Data, Biological Specimens, and Imaging Data must be included in every IRB and Ethics applications:

Clinical Data is renewable therefore scientists will have open access to such de-identified data by request to the Track-HD Steering committee. Family History Data is renewable therefore scientists will have open access to such de-identified data by request to the Track-HD Steering committee through the Clinical Trial Manager.

Biological Specimens may be renewable (e.g., DNA, cell lines) or limited (e.g., plasma, urine). Scientists will have open access to de-identified renewable biological specimens subject to compliance with reasonable material transfer procedures. The use of limited biological specimens will be subject to scientific review by the Track-HD Steering committee and the EHDN Registry steering committee to ensure that these scarce resources are put to their best use.

Imaging Data

The goal of the project is analysis of large, longitudinal datasets collected by multiple investigators. Each subject will be assigned pseudonymised research identifier. The link between the research identifier and the original subject identifier will be held at the individual study centres with the usual safeguards that are applied to all confidential information. The original subject identifier will never be known to external investigators.

The datasets will not include the subject's name, their street address, phone/fax numbers, email address, medical record number, account numbers, certificate/license numbers, vehicle identifiers including license plates, device identifiers and serial numbers, URLs, internet protocol addresses, and biometric identifiers. Additionally, any regional or cultural specific identification mechanisms (Social Security number, health plan beneficiary numbers, in the USA; NHS Numbers in UK, France, Netherlands, Canada; etc.) will also not be included. However, the date of the research scan will be included to maintain longitudinal information in the data.

All scientists requesting access to existing Track-HD data or biological specimens will be required to submit the following the EHDN data access policy.

- the investigator's biographical sketch
- a synopsis of the proposed study

- evidence of IRB approval or an IRB approved waiver for the proposed study
- statement of Research Intent and Assurance

5.20 Track-HD translation and coordination

All assessments will be translated and standardised across language areas. EHDN has the required infrastructure for translation and the expertise of the Predict-HD team will also be invaluable in attaining this. Language area coordinators will oversee this process and act as liaisons between central study coordination and centres within each language area.

Translation and cross-language validation will be overseen by Julie Stout and Marie-Noëlle Witjes-Ane.

Steps for Translation of Tests

1. For each test, it is essential to ensure that appropriate permissions and contracts are in place to make the translations. Thus, before starting the translation process, it is necessary to determine where to purchase any commercially available tests, and also what intellectual property rights and copyrights exist and therefore must be respected.
2. If dealing with a measure that involves verbal stimuli (e.g., list learning tasks), review manuals & literature that describe how the task was developed – additional procedures may be needed to select stimuli with comparable frequency, etc.
3. Identify an appropriate translator, ideally someone that is familiar with the material to be translated (e.g., neuropsychologist, psychiatrist)
4. Translator makes an initial translation; it is useful at this stage to have this initial translation reviewed briefly by one or more native speakers of the translated material, and to revise as needed.
5. The measure should be piloted in 5-10 mock participants. Pilot participants should be asked for feedback on the test. Before proceeding, mock participant performance should be reviewed for range and to ensure it is close to what would be expected. The translation should be revised as needed based on feedback and data from mock participants.
6. Final pilot testing on the instrument should occur to check for clarity of the language and cultural sensitivity and to assess similarity of norms and other psychometric issues.
7. The translated test should be sent to the source (i.e., company that sells the test, investigator who originated the test) so that the test translation can be formally documented.

6 Participant information and consent

The sheets given here are suggestions for information and consent sheets. They will be tailored to local IRB guidelines.

6.1 Study information sheet for patients

Name of study: Track-HD

Dear Participant,

You either have Huntington's disease (HD) or carry the HD gene. You are being invited to participate in Track-HD, a study being run at several centres throughout the world. The study aims to understand HD better and to improve the tools we can use to follow the course of the disease.

What is involved?

If you agree to take part, you will be asked to attend three assessments 12 months apart, over two years.

Each assessment lasts about half a day, with plenty of time for refreshments, lunch and breaks.

At each study visit, you will have a number of assessments, performed by experienced professionals.

- You will have a medical interview asking about your health, your medical history, medications and Huntington's disease in you and your family.
- You will have an interview and a questionnaire asking about your mood and other aspects of how HD may affect your behaviour. To provide a clear picture of how HD is affecting you, we may also ask a carer, friend or relative to provide information about this as well.
- A brief neurological examination will be performed, which is designed to show up and help us measure any physical effects of the disease.
- You will be asked to perform a number of automated tests, such as repeatedly pressing a button and measurement of the strength of your tongue and grip.
- You will be asked to donate a blood sample.
- Your thinking will be assessed by a series of cognitive tasks.
- You will have an oculomotor (eye movement) assessment performed. This involves using a special set of head-mounted goggles to measure your eye movements in response to computer-controlled targets projected onto a screen. It lasts about 30 minutes and carries no risk.
- An MRI brain scan will be performed, lasting about 20 minutes.

What will happen to the results of these assessments?

The results of these examinations will be entered onto an electronic database.

Your confidentiality is very important to us. Your name, address or any other information which could allow personal identification will never be recorded in the electronic database. Your data will be recorded under a code-number (or 'pseudonym'). Therefore, nobody but the local study team knows your identity or can trace your code-number back to your real name.



Data entry and the use of the Track-HD database will be carried out over the internet using secure connections. The database is held at Central Coordination, Ulm University Hospital, Ulm, Germany. Some data, such as your MRI brain scan, will be held in approved, secure storage databases elsewhere in Europe and the USA. Evaluation and publication of study results will be carried out anonymously and in the form of statistics. None of your personal data will ever be made public.

By signing the consent form you are authorizing the use of your data for large scale, multi-centre studies that will combine data from similar populations. These multi-centre studies are being conducted by the Huntington's Disease Neuroimaging Initiative (HDNI), a neuroscience consortium of universities and research institutes. Your data will be stored with a coded research identifier to protect your identity. Only pseudonymised data, which does not include anything that might directly identify you, will be shared with HDNI members and the general scientific community for research purposes. This data will be entered into linked databases at the University of California, Los Angeles and the University of Ulm, Germany to be used from this date and going forward.

What is an MRI brain scan?

Magnetic resonance imaging (MRI) is a painless and safe technique that can obtain detailed pictures of the brain. It uses magnetic fields to generate the pictures and, unlike X-ray techniques, there is no ionising radiation. MRI scans are not done on people with certain metal implants (such as pacemakers). There are no known risks to you or others. The scan itself will take about 30 minutes of your time and you won't be in the scanner for longer than about 20 minutes.

We will ask you questions to find out whether there are any reasons why you should not have a brain scan, for example if you have a pacemaker or metal implants or if you are claustrophobic. If you are able and happy to be scanned then we will continue with the study; if you are not able to be scanned for any reason then you will not have to participate any further.

What is involved in the cognitive tasks?

You will spend about an hour doing some thinking tasks, which will include for example, trying to remember some pencil and paper tasks. These are measures of how you think, and the tasks are different, to assess different areas of thinking. Some of the tasks are performed using a computer but you do not need to have any knowledge of computers in order to do them.

Why am I being asked for a blood test?

One of the aims of Track-HD is to try and find blood or urine test that will help us track the progression of disease in HD. This will be important as therapies become available for testing in patients. A blood test may let us know whether a possible therapy is effective in a particular patient.

At each visit, we will ask you to donate a sample of blood for this purpose. We would need about 50ml (3 tablespoons) of blood, which would be taken in the usual way from a vein in your arm.

A "cell line" will be created using your white blood cells. This is a technique used to keep cells alive for long periods so that they can be used to provide DNA for research.

The blood test is not like clinical tests you may have had: the significance of any results is not known and you will not receive a result from the test.

**Will my blood be tested for the HD genetic mutation?**

Only people who have already had a test for the HD mutation through an HD clinic will have the test repeated by our central laboratory in Italy. We repeat the test to obtain information about the size of the genetic abnormality. This information is used in our statistical analysis but does not usually reveal anything of clinical significance to an individual. The result of the test will not routinely be made available to you.

Who is running and funding Track-HD?

Track-HD is funded by the High Q Foundation, Inc., an American charity founded in 2002 with the aim of finding treatments for HD. In Europe, Track-HD is coordinated by the European Huntington's Disease Network (EHDN). EHDN is a scientific network of doctors and scientists committed to HD research.

Are there any risks involved?

No treatments will be given, and there are no specific risks involved.

Some people experience claustrophobia when having an MRI scan, but we will do whatever we can to help you relax before and during the scan.

With the blood tests, there is some minor discomfort, and a small risk of bruising or bleeding with this procedure. Some people feel faint or light-headed when having blood taken. If this happens, you will be asked to lie down until you feel better.

Will taking part cost me anything?

All travel expenses for you and anyone accompanying you will be refunded, and we will also pay for lunch and snacks on the day of study visits.

Will I profit from participating?

There is no personal financial gain to yourself now or in the future should this research result in a biomarker being developed for use in HD therapy trials, even if this involves collaboration with a commercial company.

Do I have to take part?

No. Participation in the study is entirely voluntary and you are free to withdraw at any time without giving a reason. If you decide not to take part, or to withdraw, your clinical care will not be influenced in any way. Your legal rights are not affected by participating in the study and the study is indemnified.

Will I be told the results of my assessments and scans?

We will not usually tell you what the results of your assessments are, because these are not assessments that are for your clinical care. If you would like to see one of your brain scans this can usually be arranged on the day with the radiographer. We will not usually tell you whether your results have changed from one visit to the next. If any aspect of the assessment worries you, we can arrange for you to be referred to an appropriate specialist to investigate this further, through clinic. We would also like your agreement that we would inform you and your GP in the unlikely event that one of the scans revealed something unexpected and important, such as a brain haemorrhage.

Once the study is finished, you will be told about the overall results of the study, which will be about the group as a whole rather than individuals.



Are there any restrictions on what I can eat or do?

We ask that you do not drink any alcohol during the day or evening before a study visit. Otherwise, there are no restrictions.

Will taking part affect my treatment or medication?

No, any treatment would continue as normal.

Will the study team contact me?

We will ask your permission to contact you between visits, to clarify any questions with you, to provide you with updates and to arrange your next visit. We will ask how and when you would like to be contacted.

Who can I contact for more information?

You may contact (name of investigator) on (telephone number).

Ethical review statement

This research project has been reviewed and approved by the (name of body) Ethics Committee.

Compensation arrangements

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns of this study, the normal National Health Service complaints mechanisms should be available to you.

Confidentiality and data protection statement

All staff involved in looking after you during this clinical study are bound by medical confidentiality and are obliged to comply with data protection legislation. Research results relating to this study are intended for use in an anonymous form in scientific publications. As far as is necessary for ensuring correct data entry, authorised individuals (e.g. the sponsor, the university) are permitted to review your medical records. If individuals authorized to view records are not bound by medical confidentiality as mentioned above, personal data that come to their attention during checks are confidential under the Data Protection Act.

(Name of the site director)

(Place, date)



6.2 Study information sheet for control subjects

Name of study: Track-HD

Dear Participant,

You are the partner, spouse or carer for someone with the Huntington's disease gene, or you were at risk of inheriting HD and have had a negative test for the mutation.

You are being invited to participate as a control subject in Track-HD, a study being run at several centres throughout the world. The study aims to understand HD better and to improve the tools we can use to follow the course of the disease. As a control subject, you will do the same assessments as an HD patient.

What is involved?

If you agree to take part, you will be asked to attend three assessments 12 months apart, over two years.

Each assessment lasts about half a day, with plenty of time for refreshments, lunch and breaks.

At each study visit, you will have a number of assessments, performed by experienced professionals.

- You will have a medical interview asking about your health, your medical history, and medications.
- You will have an interview and a questionnaire asking about your mood and other aspects of your behaviour. We may also ask a friend or relative to provide information about this as well.
- A brief neurological examination will be performed, which is designed to show up and help us measure any physical effects of the disease.
- You will be asked to perform a number of automated tests, such as repeatedly pressing a button and measurement of the strength of your tongue and grip.
- You will be asked to donate a blood sample.
- Your thinking will be assessed by a series of cognitive tasks.
- You will have an oculomotor (eye movement) assessment performed. This involves using a special set of head-mounted goggles to measure your eye movements in response to computer-controlled targets projected onto a screen. It lasts about 30 minutes and carries no risk.
- An MRI brain scan will be performed, lasting about 20 minutes.

What will happen to the results of these assessments?

The results of these examinations will be entered onto an electronic database.

Your confidentiality is very important to us. Your name, address or any other information which could allow personal identification will never be recorded in the electronic database. Your data will be recorded under a code-number (or 'pseudonym'). Therefore, nobody but the local study team knows your identity or can trace your code-number back to your real name.



By signing the consent form you are authorizing the use of your data for large scale, multi-centre studies that will combine data from similar populations. These multi-centre studies are being conducted by the Huntington's Disease Neuroimaging Initiative (HDNI), a neuroscience consortium of universities and research institutes. Your data will be stored with a coded research identifier to protect your identity. Only pseudonymised data, which does not include anything that might directly identify you, will be shared with HDNI members and the general scientific community for research purposes. This data will be entered into linked databases at the University of California, Los Angeles and the University of Ulm, Germany to be used from this date and going forward.

Data entry and the use of the Track-HD database will be carried out over the internet using secure connections. The database is held at EHDN Central Coordination, Ulm University Hospital, Ulm, Germany. Some data, such as your MRI brain scan, will be held in approved, secure storage databases elsewhere in Europe and the USA. Evaluation and publication of study results will be carried out anonymously and in the form of statistics. None of your personal data will ever be made public.

What is an MRI brain scan?

Magnetic resonance imaging (MRI) is a painless and safe technique that can obtain detailed pictures of the brain. It uses magnetic fields to generate the pictures and, unlike X-ray techniques, there is no ionising radiation. MRI scans are not done on people with certain metal implants (such as pacemakers). There are no known risks to you or others. The scan itself will take about 30 minutes of your time and you won't be in the scanner for longer than about 20 minutes.

We will ask you questions to find out whether there are any reasons why you should not have a brain scan, for example if you have a pacemaker or metal implants or if you are claustrophobic. If you are able and happy to be scanned then we will continue with the study; if you are not able to be scanned for any reason then you will not have to participate any further.

What is involved in the cognitive tasks?

You will spend about an hour doing some thinking tasks, which will include for example, trying to remember some words, naming pictures, and some pencil and paper tasks. These are measures of how you think, and the tasks are different, to assess different areas of thinking. Some of the tasks are performed using a computer but you do not need to have any knowledge of computers in order to do them.

Why am I being asked for a blood test?

One of the aims of Track-HD is to try and find blood or urine test that will help us track the progression of disease in HD. This is important as therapies become available for testing in patients. A blood test may let us know whether a possible therapy is effective in a particular patient.

At each visit, we will ask you to donate a sample of blood for this purpose. We would need about 50ml (3 tablespoons) of blood, which would be taken in the usual way from a vein in your arm.

A "cell line" will be created using your white blood cells. This is a technique used to keep cells alive for long periods so that they can be used to provide DNA for research.

The blood test is not like clinical tests you may have had: the significance of any results is not known and you will not receive a result from the test.

Will my blood be tested for the HD genetic mutation?

As a control subject, your blood will not be tested for the HD genetic mutation.



Who is running and funding Track-HD?

Track-HD is funded by the High Q Foundation, Inc., an American charity founded in 2002 with the aim of finding treatments for HD. In Europe, Track-HD is coordinated by the European Huntington's Disease Network (EHDN). EHDN is a scientific network of doctors and scientists committed to HD research.

Are there any risks involved?

No treatments will be given, and there are no specific risks involved.

Some people experience claustrophobia when having an MRI scan, but we will do whatever we can to help you relax before and during the scan.

With the blood tests, there is some minor discomfort, and a small risk of bruising or bleeding with this procedure. Some people feel faint or light-headed when having blood taken. If this happens, you will be asked to lie down until you feel better.

Will taking part cost me anything?

All travel expenses for you and anyone accompanying you will be refunded, and we will also pay for lunch and snacks on the day of study visits.

Will I profit from participating?

There is no personal financial gain to yourself now or in the future should this research result in a biomarker being developed for use in HD therapy trials, even if this involves collaboration with a commercial company.

Do I have to take part?

No. Participation in the study is entirely voluntary and you are free to withdraw at any time without giving a reason. If you decide not to take part, or to withdraw, your clinical care will not be influenced in any way. Your legal rights are not affected by participating in the study and the study is indemnified.

Will I be told the results of my assessments and scans?

We will not usually tell you what the results of your assessments are, because these are not assessments that are for your clinical care. If you would like to see one of your brain scans this can usually be arranged on the day with the radiographer. We will not usually tell you whether your results have changed from one visit to the next. If any aspect of the assessment worries you, we can arrange for you to be referred to an appropriate specialist to investigate this further, through clinic. We would also like your agreement that we would inform you and your GP in the unlikely event that one of the scans revealed something unexpected and important, such as a brain haemorrhage.

Once the study is finished, you will be told about the overall results of the study, which will be about the group as a whole rather than individuals.

Are there any restrictions on what I can eat or do?

We ask that you do not drink any alcohol during the day or evening before a study visit. Otherwise, there are no restrictions.

Will taking part affect my treatment or medication?

No, any treatment would continue as normal.

**Will the study team contact me?**

We will ask your permission to contact you between visits, to clarify any questions with you, to provide you with updates and to arrange your next visit. We will ask how and when you would like to be contacted.

Who can I contact for more information?

You may contact (name of investigator) on (telephone number).

Ethical review statement

This research project has been reviewed and approved by the (name of body) Ethics Committee.

Compensation arrangements

If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns of this study, the normal National Health Service complaints mechanisms should be available to you.

Confidentiality and data protection statement

All staff involved in looking after you during this clinical study are bound by medical confidentiality and are obliged to comply with data protection legislation. Research results relating to this study are intended for use in an anonymous form in scientific publications. As far as is necessary for ensuring correct data entry, authorised individuals (e.g. the sponsor, the university) are permitted to review your medical records. If individuals authorized to view records are not bound by medical confidentiality as mentioned above, personal data that come to their attention during checks are confidential under the Data Protection Act.

(Name of the site director)

(Place, date)



6.3 Study information sheet for companions

Dear Participant,

You are a companion of a person affected by Huntington's disease (HD) (either a patient or a presymptomatic mutation carrier) who has asked you whether you are willing to assist in a research project called Track-HD. This is a study being run at several centres throughout the world. The study aims to understand HD better and to improve the tools we can use to follow the course of the disease. We hope this will help us design future clinical trials of therapies for HD.

Since the symptoms of HD are noticed differently by companions and the affected persons themselves, and the disease of a close one also has an impact on companions, we would like to ask you to complete 3 questionnaires about your spouse/partner at each visit. These questionnaires ask any mood symptoms that your spouse/partner may suffer from.

The completed questionnaires will be entered onto an electronic database which is available to the network.

Your name, address or any other information which could allow personal identification will not be recorded in the database. The results of these examinations will be entered onto an electronic database.

Your confidentiality is very important to us. Your name, address or any other information which could allow personal identification will never be recorded in the electronic database. Your data will be recorded under a code-number (or 'pseudonym'). Therefore, nobody but the local study team knows your identity or can trace your code-number back to your real name.

Data entry and the use of the Track-HD database will be carried out over the internet using secure connections. The database is held at Central Coordination, Ulm University Hospital, Ulm, Germany. Evaluation and publication of study results will be carried out anonymously and in the form of statistics. None of your personal data will ever be made public.

If you are willing to participate it is important that you, as a companion, attend follow-up examinations once a year for three years.

Evaluation and publication of study results will be carried out anonymously and in the form of statistics. As a result, none of your personal data will ever be made public.

Track-HD is funded by the High Q Foundation, Inc., an American charity founded in 2002 with the aim of finding treatments for HD. In Europe, Track-HD is coordinated by the European Huntington's Disease Network (EHDN). EHDN is a scientific network of doctors and scientists committed to HD research.

Volunteering

Your participation in this research project is voluntary. **You are free to withdraw from the study at any time and without giving reason.**

Insurance

Because Track-HD is neither a drug or pharmacological study, there are no additional health risks.

Confidentiality/data protection

All clinicians and related medical staff involved in looking after you and the affected person during this clinical study abide by medical confidentiality and are obliged to comply with data protection. Research results relating to this study are intended for use in an anonymous form in scientific publications.



As far as is necessary for ensuring correct data entry, authorized individuals (e.g. the sponsor, the university) are permitted to review the medical records.

If individuals authorized to view records are not bound by medical confidentiality as mentioned above, personal data that come to their attention during checks are confidential under the Data Protection Act.

Contact

Should you have any questions relating to this study, you may contact any of the below during normal working hours

Attached: Copy of the information sheet supplied to patients for Track-HD.

6.4 Data protection information

This sheet gives you more information about the use of your data for the Track-HD study.

An essential safety aspect of the project is the processing of my data in a pseudonymised manner. What does that mean and how is it carried out?

During your first visit, your clinician will enter certain data about you into the computer. From these personal data a unique code-number ('pseudonym') is calculated, consisting of a series of 9 digits. The following personal data are used: first name, birth name (surname), date of birth, place of birth and mother's maiden name.

Example:

Jane Smith née Jones, born 10.11.1964 in London, mother's maiden name Taylor.

This information results in the code-number ('pseudonym') 425-491-326.

Importantly, the pseudonym is created on the basis of a so-called 'secure hash-algorithm'. A unique value is created from your data by a complex one-way procedure. The mathematical algorithm used ensures that nobody (not even the system programmer) can use the pseudonym to work out your personal data.

The personal data transmitted to generate the pseudonym are held only for the calculation of your pseudonym in the working memory of a large computer ('server'). The calculation of the pseudonym requires a very short time (a fraction of a second). Viewing personal data during this time is impossible. After that, all data used to create the pseudonym are permanently erased from the working memory of the server so that no identifying details remain. Data used to generate the pseudonym are never stored in any form of permanent memory (e.g. on the hard drive). Following this, all database entries and every use of data are exclusively carried out under the assigned pseudonym.

Who can see and use my data?

1. **You.** If you wish so, the clinician treating you can let you to see all data stored about you. It is advised that you review these data together with the physician treating you to explain medical terms to you, and to answer questions you may have.
2. **Your local study team.** The study team enrolling you for Track-HD are the only people apart from yourself who can link your pseudonym to your personal data. After generation of the pseudonym, all entry of clinical information in the data base is carried out under your pseudonym. The study site team, including your treating clinician, can view all clinical data recorded under pseudonym.
3. **EHDN staff.** EHDN staff can view the data stored under your pseudonym. This is necessary to ensure correct documentation and high data quality. For the purpose of data control, staff of EHDN ('monitors' and 'auditors') are allowed to check with your study site team that the data entered onto the network matches the data found in your medical records. Monitors and auditors are bound by medical confidentiality.
4. **Authorised researchers.** Scientists/clinicians who are involved in HD research can apply to the scientific review board of Track-HD (a group of experienced clinicians and scientists) for authorisation to obtain access to the database. Authorized researchers can only view coded data. To ensure the highest degree of confidentiality, pseudonyms are changed before the data bank is made available to authorized researchers. This guarantees that all publications reporting on the findings of authorised research use anonymised data.
5. **System administrators.** In order to safeguard the EHDN central database, a small number of authorised system administrators can view pseudonymised data.

How can I be sure that unauthorised people cannot gain access to my data while they are sent via the Internet?

All data travelling via the internet are encrypted, in a manner similar to how credit card transactions are securely transmitted by the internet. For all practical purposes, nobody aside from the intended receiver can read or access these data. The server where the database is stored is located behind a 'firewall'. This sophisticated security system ensures that only authorised computers and individuals can gain access to the database. Furthermore, the central database does not contain identifying data, as all data are stored under a pseudonym.

How long are my data stored for?

All data will be stored for the foreseeable future, i.e. for the next two generations (50 years) or until an efficient therapy for HD is established. Complete deletion of all data is difficult, since data are likely to have become part of scientific studies and therefore need to be kept on record, even years after the research was completed. However, if you wish, all links to you can be deleted and irreversibly destroyed. If this is done, not even the physicians chosen by you for enrolment into Track-HD will be able to recognize data as belonging to you. This anonymisation will be carried out in the following cases:

- If you withdraw your consent for further participation in TRACK-HD and if you request that your past data are anonymised.
- If you request complete anonymisation of your data

(Name of the consenting clinician)

(Location, date)



6.5 Consent form for patients

Name of study: Track-HD

Initial each box

Study information

The content, procedures, risks and aims of the research project named above as well as the procedures for handling my data have been explained to me in detail by the researcher named below.

I have had the opportunity to ask questions and obtained answers which I felt were satisfactory.

☐

I have had sufficient time to decide whether or not I want to participate in the project.

My participation is entirely voluntary and participation will not affect my legal rights.

I have received a copy of the patient information sheet.

Medical records

I give my permission for members of the local study team to view my medical records.

☐

Blood sample donation

I give my permission for the collection of blood (up to 50ml) from me at each study visit and agree to donate it for studies to identify markers of Huntington's disease (HD) sponsored by the High Q Foundation, Inc. (Sponsor). I understand that my samples are submitted to and stored at a central Biorep repository located in Milan (Italy) or New York for the next two generations (50 years) or until an efficient therapy for HD is established. I can contact my study site at any time and can request destruction of the samples stored from me.

☐

HD genetic test

I give my permission for an HD mutation analysis on my DNA.

☐

I understand that this result is for research only and that the result will not routinely be made available to me.

Creation of cell line

I give permission for a cell line to be established from my blood cells and kept for 50 years or until a therapy for HD is found. They will be kept as a source of DNA for HD genetic research including research sponsored by the Sponsor. I can request destruction of the cell line at any time.

☐



Data protection and Data Sharing

I agree that data obtained during the course of this study can be recorded in questionnaires and in electronic form, processed without providing personal identity and stored in pseudonymised form at a secure server located at the University of Ulm, Germany. In addition, some data will be stored at other secure, authorised study sites.

I agree to the storage of imaging data derived from MRI scans and pseudonymised data at the central repository of the Huntington's Disease Neuro-Imaging Initiative (HDNI) server in Los Angeles, USA.

I agree that the imaging data derived from MRI scans and pseudonymised data will be shared with the Sponsor.

By signing the consent form I am authorizing the use of my data, genetic information, imaging scans and biosamples for HD research sponsored by the Sponsor for large scale, multi-centre studies. Such HD research and multi-centre studies are being conducted by the Track-HD research team and other qualified HD researchers including the HDNI. Your data will be stored with a coded research identifier to protect your identity. Only pseudonymised data, biosamples and imaging scans, which does not include anything that might directly identify you, will be shared with the Sponsor, other HD researchers and the general scientific community for research purposes. These data will be entered into linked databases at the University of California, Los Angeles and the University of Ulm, Germany to be used from this date and going forward.

☐

I agree that authorised persons bound by confidentiality can view the personal data recorded as far as it is necessary or legally required for data control. **For this purpose only**, I exempt the clinician from the obligation to ensure medical confidentiality at all times.

Contact between visits

I give my permission for my study site team to contact me between visits:

- to clarify questions (e.g. concerning my answers in Track-HD questionnaires);
- to provide me with updates on Track-HD; or
- to arrange future study assessments.

☐

Video recording

I consent to the video recording of the cognitive, clinical and neuropsychiatric components of the assessment, the transmission of these recordings via secure internet connection and their viewing by authorised personnel for quality control, research and training purposes.

☐

I agree to take part in this study.

☐

Name of participant

Signature of participant

Date

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Name of researcher

Signature of researcher

Date

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6.6 Consent form for control subjects

Name of study: Track-HD

Initial each box

Study information

The content, procedures, risks and aims of the research project named above as well as the procedures for handling my data have been explained to me in detail by the researcher named below.

I have had the opportunity to ask questions and obtained answers which I felt were satisfactory.

☐

I have had sufficient time to decide whether or not I want to participate in the project.

My participation is entirely voluntary and participation will not affect my legal rights.

I have received a copy of the patient information sheet.

Medical records

I give my permission for members of the local study team to view my medical records.

☐

Blood sample donation

I give my permission for the collection of blood (up to 50ml) from me at each study visit and agree to donate it for studies to identify markers of Huntington's disease (HD) sponsored by the High Q Foundation, Inc. (Sponsor). I understand that my samples are submitted to and stored at a central Biorep repository located in Milan (Italy) or New York for the next two generations (50 years) or until an efficient therapy for HD is established. I can contact my study site at any time and can request destruction of the samples stored from me.

☐

Creation of cell line

I give permission for a cell line to be established from my blood cells and kept for 50 years or until a therapy for HD is found. They will be kept as a source of DNA for HD genetic research including research sponsored by the Sponsor. I can request destruction of the cell line at any time.

☐



Data protection and Data Sharing

I agree that data obtained during the course of this study can be recorded in questionnaires and in electronic form, processed without providing personal identity and stored in pseudonymised form at a secure server located at the University of Ulm, Germany. In addition, some data will be stored at other secure, authorised study sites.

I agree to the storage of imaging data derived from MRI scans and pseudonymised data at the central repository of the Huntington's Disease Neuro-Imaging Initiative (HDNI) server in Los Angeles, USA.

I agree that the imaging data derived from MRI scans and pseudonymised data will be shared with the Sponsor.

By signing the consent form I am authorizing the use of my data, genetic information, imaging scans and biosamples for HD research sponsored by the Sponsor for large scale, multi-centre studies. Such HD research and multi-centre studies are being conducted by the Track-HD research team and other qualified HD researchers including the HDNI. Your data will be stored with a coded research identifier to protect your identity. Only pseudonymised data, biosamples and imaging scans, which does not include anything that might directly identify you, will be shared with the Sponsor, other HD researchers and the general scientific community for research purposes. These data will be entered into linked databases at the University of California, Los Angeles and the University of Ulm, Germany to be used from this date and going forward.

☐

I agree that authorised persons bound by confidentiality can view the personal data recorded as far as it is necessary or legally required for data control. **For this purpose only**, I exempt the clinician from the obligation to ensure medical confidentiality at all times.

Contact between visits

I give my permission for my study site team to contact me between visits:

- to clarify questions (e.g. concerning my answers in Track-HD questionnaires);
- to provide me with updates on Track-HD; or
- to arrange future study assessments.

☐

Video recording

I consent to the video recording of the cognitive, clinical and neuropsychiatric components of the assessment, the transmission of these recordings via secure internet connection and their viewing by authorised personnel for quality control, research and training purposes.

☐

I agree to take part in this study.

☐

Name of participant

Signature of participant

Date

.....

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Name of researcher

Signature of researcher

Date

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6.7 Consent form for companions

Name of study: Track-HD

Initial each box

Study information

I have received a copy of the companion information sheet and had time to read it

The content, procedures, risks and aims of the research project named above as well as the procedures for handling my data in the companion questionnaires have been explained to me in detail by the researcher named below.

I have had the opportunity to ask questions and obtained answers which I felt were satisfactory. ☐

I have had sufficient time to decide whether or not I want to participate in the project.

My participation is entirely voluntary and participation will not affect my legal rights.

Contact between visits

I give my permission for my study site team to contact me between visits:

- to clarify questions (e.g. concerning my answers in Track-HD questionnaires);
 - to provide me with updates on Track-HD; or
 - to arrange future study assessments.
- ☐

Data protection

I agree that data obtained during the course of this study can be recorded in questionnaires and in electronic form, processed without providing personal identity and stored in pseudonymised form at a secure server located at the University of Ulm, Germany. In addition, some data will be stored at other secure, authorised study sites. ☐

I agree that authorised persons bound by confidentiality can view the personal data recorded as far as it is necessary or legally required for data control. **For this purpose only**, I exempt the clinician from the obligation to ensure medical confidentiality at all times.

I agree to take part in this study. ☐

Name of participant

Signature of participant

Date

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Name of researcher

Signature of researcher

Date

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6.8 Risk Assessment for harm to self or others

All personnel involved in the Track HD assessments will be informed of the risk indicators and protocols outlined below.

Self harm/Suicide

Any of the following occurrences will initiate the Suicide Risk Assessment Protocol outlined below:

1. A total score of ≥ 24 on the BDI II
2. Endorsement of the suicide item on the BDI II: at the level 3 ("I would like to kill myself") or level 4 ("I would kill myself if I had the chance).
3. PBA suicidal thoughts item (total score of ≥ 9)
4. Mention of suicide plans during any part of the Track-HD assessment day
5. Reports of concern regarding significant depressive symptoms from a care-giver/partner

Harm To Others

Any of the following occurrences will initiate the harm to others assessment protocol outlined below:

1. Report by care-giver/partner in the Irritability and Aggression Diary that they or someone else has been physically abused by the HD subject. Diary ratings must be reviewed before the subject leaves the Track-HD assessment day.
2. Report during the PBA or any part of the Track-HD assessment day that physical abuse (threatened or actual) has occurred
3. Report by partner/caregiver that they fear for their safety as a result of the HD subject's irritability and aggression.

Suicide/Harm to Others Risk Assessment Protocol

1. Each site will designate a primary licensed professional (e.g. neurologist, psychiatrist, clinical psychologist, HD nurse specialist, psychiatric nurse or clinical social worker) to further assess suicide risk or potential risk to others identified during screening. If unavailable, a suitable back-up must be provided. For most sites this should be the site PI and back-up support must be organised during periods of absence.
2. Further actions will depend on the discretion of the clinician but may include but are not limited to one or more of the following:
 - Determination that no further action is required
 - Follow-up phone contact
 - Referral to mental health services for further assessments
 - Follow-up at local HD clinic
 - Consultation with a family member
 - Immediate inpatient or outpatient treatment
 - Notification of law enforcement
3. Any initiation of this protocol must be documented and enforced by the site PI. If any Track-HD subject requires urgent in patient treatment or notification of law enforcement, the Track HD clinical trial manager and the Track-HD study PI (SJT) must be notified. This, as well as other reportable events, will be reviewed by clinicians on the Track HD executive and steering committee on a semi-annual basis to ensure continuing effectiveness of screening procedures and assessment/treatment protocols.

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