EURO **HUNTINGTON'S DISEASE** NETWORK

REGISTRY
Study Protocol
Version 2.0

Amendment 1 replacing version 1.0
(version 2.0 includes two new, optional components:
'donation of biosamples' and 'family history questionnaire')

REGISTRY – an observational study of the European Huntington-Disease Network (EHDN)

Version 2.0
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Protocol Version 2.0. Table of content

1. Overview/summary

Protocol Title
REGISTRY

Type of Study:
Prospective observational study with no experimental treatment

Steering committee
See appendix C

Study centres
Contributing study sites throughout Europe (currently 100 centres)

Study period
Prospective, open-ended study. Participants are asked at the time of signing up for REGISTRY (= at the base line visit) to attend as many annual follow up visits as possible

Study objectives
To collect prospective data on the phenotypical characteristics of Huntington's disease (HD) mutation carriers regardless of whether they display clinical symptoms and signs of HD and of individuals who are part of an HD family (irrespective of their mutation carrier status), in order

- to obtain natural history data on a wide spectrum of HD patients, HD mutation carriers and individuals who are part of an HD family
- to relate phenotypical characteristics
    - with genetic factors ('genetic modifiers'),
    - with data derived from the study of body fluids (blood, urine – 'wet biomarker') and
    - imaging data ('dry biomarker')
- to expedite identification and recruitment of participants for clinical trials
- to plan for future research studies (observational and interventional trials aimed at better symptom control or aimed at slowing or postponing the onset and progression of HD).

To achieve these objectives, participants are asked to donate biosamples (blood and urine) for studies to identify genetic modifiers of HD and to establish and validate biological markers tracking the progressive course of HD; in this context a family history is requested as well in order to understand the relationships of clinical data sets and biosamples from related donors. In addition, non-mutation carrying family members of participants are asked to consider donating biosamples to serve as controls.

Study population
Participants will either have signs and symptoms of HD, be a member of an HD family or are know to carry the HD mutation. Whilst there are no age restrictions, all participants must either be able to provide consent or have a parent/guardian who can provide parental permission, or have an authorized representative who can provide consent.

Study design
REGISTRY consists of 3 components

a) a clinical phenotypical characterization
b) the collection of biological specimen
c) the collection of family history data

At the **baseline study visit**, the following will take place:

a) Clinical phenotypical characterization
The clinical phenotype will be assessed and documented based on information obtained from three sources:

- trained raters (e.g. neurologists, psychiatrists, neuropsychologists etc.) who record their clinical impression using the Unified Huntington's Disease Rating Scale (UHDRS'99) and the Hamilton Depression Rating Scale (HDRI)
- affected/HD mutation carrier/person at risk for HD who self-report on their perceived quality of life (SF-36), their mood (Beck's Depression Inventory - BDI) and on the economic impact HD has on their lives (Client Services Receipt Inventory - CSRI)
- companions/care-givers (if available) who record the impact of HD/mutation carrier status/at risk status on the families/social core units (Care Giver Questionnaire - CGQ)

b) Donation of biological specimens – 30 ml of blood and 30 ml of urine.
The biological specimens are donated with the understanding that all specimens are used for HD related research and that they are stored at a central bio-repository.

c) Completion of a family history questionnaire (FHQ).
All participants with a family history of HD will be invited to participate. The FHQ collects information about the history of HD within a family unit and will therefore focus on the side of the family affected by HD. Within the FHQ data on 3 generations will be assembled as well as data on the spouse. The purpose of the FHQ is (1) to obtain a family tree as an important part of standard medical care and (2) to render linked biosamples or data sets identifiable while protecting the privacy of all donors. In order to obtain linked biosamples and linked clinical data sets participants are asked – provided that the feel comfortable to do so - to hand out to their relatives an invitation to consider participation in REGISTRY.

Finally, participants are asked to indicate whether they agree to be contacted by the study site in-between annual study visits to collect additional information, to provide information regarding REGISTRY or on upcoming intervention studies for which participants in REGISTRY may be eligible in order to allow them to consider their participation.

At each **annual follow up study visit**, the following will take place:

a) a clinical phenotypical characterization identical to the one at base line visit. As part of the UHDRS'99, information about events which have occurred since the last visit (e.g. changes in occupation, intercurrent health problems, changes in medication etc.) will be recorded.

Participants who consented to donate biological specimens and to volunteer the family history will be requested
b) to donate a next sample of biological specimens (30 ml of blood and 30 ml of urine)
c) to update the FHQ: participants will be asked to provide information about new deaths and onsets of HD.

All participants will be given the opportunity to re-evaluate their decisions regarding participation in the optional components of REGISTRY.

Number of subjects
This study will include as many eligible subjects as willing to participate. We hope to recruit approximately a quarter of the estimated 40.000 HD patients residing in Europe within 7 years.

Inclusion criteria
The following individuals may be eligible to participate

- Individuals with clinical features of HD with a confirmatory family history of HD or with DNA testing results demonstrating the presence of the HD mutation (i.e. a CAG repeat expansion within the HD gene >35 on larger allele) (category 1)
- Individuals without clinical features of HD with DNA testing result demonstrating presence of the HD mutation (i.e. CAG repeat expansion within the HD gene >35 on larger allele) (category 2)
- First-degree relatives (i.e. parents, siblings, or children) of individuals with HD (category 3)
- Second-degree relatives (i.e. grandparents and grandchildren) of participating individuals with HD (category 4)
- Family members of participating individuals from category 1 or 2 who are know not to carry the HD mutation (e.g., spouses) (category 5)

Participants may be male or female and of any age. All participants must be able to provide consent for themselves, have a parent/guardian who can provide parental permission, or have an authorized legal representative who can provide consent.

Exclusion criteria

- Subjects who are unable to understand the study protocol or unable to give informed consent, and have no legal representative.
- Participants with choreic movement disorder other than HD.

Assessments and measures
For the assessment of the **clinical phenotype** the following instruments will be used:

- the Unified Huntington's Disease Rating Scale (UHDRS'99) assessing four major clinical domains of impairment: (1) motor, (2) cognitive, (3) behavioural, and (4) functional capacity,
- the Hamilton Depression Rating Scale (HDRI), a clinical rating scale to assess symptoms and signs indicative of depression and emotional impairment
- the Beck's Depression Inventory (BDI), a scale used for self-report on symptoms suggestive of depression
- a quality of life scale (SF-36),
- a scale measuring the economic impact of HD and HD related health problems, the Client Services Receipt Inventory (CSRI),
- a scale recording the impact of HD/mutation carrier status/at risk status on the families/social core units, the Care Giver Questionnaire (CGQ)

It is expected that the tools described above will be developed and complemented by additional, quantifiable measures in the future.

For the collection of **biological specimen** the procedures described above are applied.

Family history data is collected using a family history questionnaire (FHQ) The FHQ collects information about the history of HD within a family unit and will therefore focus on the side of the family affected by HD. Within the FHQ data on three generations will be assembled as well as data on the spouse. In order to link biosamples and link clinical data sets participants are asked (provided that the feel comfortable to do so) to forward an invitation to their relatives so they can consider taking part in REGISTRY.

Sample size consideration

As HD is a relatively rare disease, no single study site is in the position to obtain phenotypical (clinical) data or biosamples in sufficient numbers to conduct conclusive studies concerning the majority of questions of clinical relevance in HD. Therefore a cooperative effort throughout Europe appears an appealing avenue to provide large enough clinical data sets and sufficient numbers of biosamples to answer questions conclusively by conducting sufficiently powered studies. Obviously, the numbers need to answer scientific questions conclusively will depend on the outcomes and read-outs under consideration. For example, performing a meaningful factorial analysis to improve and condense clinical rating scales may require several hundred clinical data sets with a wide spread of phenotypical presentations. A genome-wide search for genetic modifiers may require (given present days technologies) well above 3000 samples for an informative study. At the other extreme of the spectrum, a carefully selected, small (e.g. n = 60) sample representing all clinical stages of HD may well be sufficient to strongly suggest the usefulness of a read-out from plasma as a biomarker tracking the progressive course of HD. In the future, the availability of prospectively ascertained biosamples linked to phenotypical states at the time of sample collection will permit robust conclusions about the validity of suggested biomarkers within a short time frame. Overall, data from REGISTRY should assist in determining the robustness of conclusions derived from previous studies conducted on small sample sizes using independent data sets.

2. Detailed study description

2.1 Background and rational

HD is an autosomal-dominantly inherited, progressive neurodegenerative disorder characterized clinically by a movement disorder (typically chorea), behavioural 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. By implication, genetic testing (preceded by genetic counselling according to internationally accepted guidelines) allows to determine whether a clinically normal person harbours the HD mutation and thus predict that a person will develop HD before clinical symptoms and signs develop. 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 (Ref). In addition, estimated 80,000 individuals carry the HD mutation but remain 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 [1]. Individuals who have ≥ 36 CAG repeats may develop the clinical symptoms and signs of HD including motor, cognitive and behavioural 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.
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 [2]. Systematic screening efforts to identify compounds with disease modifying properties are under way [3, 4] and some compounds have been reported to result in beneficial effects when applied in model systems of HD [5] thus providing a rational for identifying well tolerated and clinical effective novel treatments for HD. However, currently the predictive value of these promising results obtained in model systems for HD patients are unknown. In addition, incremental advances in clinical research on HD have been made. 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 surrogate markers which track the course of HD ('state biomarkers'), and by identifying factors that influence the onset and progression of illness.

REGISTRY is designed

- to obtain natural history data on a wide spectrum of HD patients, HD mutation carriers and individuals who are part of an HD family
- to relate phenotypical characteristics
    - with genetic factors ('genetic modifiers'),
    - with data derived from the study of body fluids (blood, urine – 'wet biomarker') and
    - imaging data ('dry biomarker')
- to expedite identification and recruitment of participants for clinical trials
- to plan for future research studies (observational and interventional trials aimed at better symptom control or aimed at slowing or postponing the onset and progression of HD).

REGISTRY integrates prospectively and systematically collected clinical research data (e.g. phenotypical clinical features, family history, demographical characteristics) with access to

biological specimens (e.g., blood, urine) obtained from individuals with manifest HD, unaffected individuals known to carry the HD mutation or at risk of carrying the HD mutation, and control research participants (e.g., spouses, siblings or offspring of HD mutation carriers known not to carry the HD mutation). Biological specimens and phenotypical data will be provided to qualified scientists whose projects are submitted to, reviewed by and approved by the Scientific Review Board of Euro-HD network and who declared in writing that they accept the policies of EHDN with respect to the use of the data/materials provided and with respect to the publication of results (see data sharing and publication policies of EHDN, attached). Research projects should aim to advance scientific knowledge towards establishing clinically effective treatments that delay onset and/or slow the progression of the disease.

REGISTRY was conceived as a long-term project to integrate clinical and preclinical research approaches to advance the experimental therapeutics of HD while ensuring the privacy and protections of consenting research participants. REGISTRY is complementary to the COHORT project of the Huntington Disease Study Group (HSG) and builds on strong collaborative relationships among basic scientists, clinical investigators and advocacy organisations for HD in the context of the European Huntington Disease Network (EHDN), an European consortium of scientists, researchers and lay organisations to improve treatment options for HD; REGISTRY was planned and is overseen by the EHDN. REGISTRY is part of the Huntington Project (http://www.huntingtonproject.org/), a worldwide collaborative undertaking to develop treatments that make a difference for HD. The Huntington Project, EHDN and REGISTRY are sponsored by the High-Q Foundation, a not-for-profit organization that supports a variety of research projects seeking to find treatments for HD.

In addition, there is some overlap with two 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 a HD parent who have unknown mutation carrier status since having chosen not to undergo DNA testing). PREDICT-HD has a European extension for some European countries (at the time of this writing Germany, Spain and the UK) whereas PHAROS does not allow participation of non-English speaking subjects nor of subjects from outside of the USA, Canada or Australia. REGISTRY will therefore provide an ongoing observational study for eligible subjects who are not able to participate in PREDICT-HD or PHAROS as well as for subjects who conclude their research participation in PREDICT-HD and PHAROS.

The steady worsening of the motor, cognitive, and behavioural 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 [6-12]. The Unified Huntington's Disease Rating Scale (UHDRS) was developed by the HSG in 1993 and revised in 1999 as UHDRS 99 [13, 14]. The UHDRS'99 assesses four major clinical domains of impairment: (1) motor, (2) cognitive, (3) behavioural, 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, which will be employed in REGISTRY, has been used in all clinical sites collaborating as Huntington Disease Study Group (HSG) in North America, Europe, and Australia. The UHDRS has undergone extensive testing of reliability and internal consistency [13-15] and has been shown to have a good inter-rater reliability for the total motor score. The

motor and cognitive sections of the UHDRS correlate 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, 0.90 for the cognitive tests, 0.83 for the behavioural component, and 0.95 for the functional component of the UHDRS [16]. The UHDRS has been used widely in HD clinical trials [17, 18].

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 [19]. 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 [1]. The unstable, expanded CAG repeat within the coding region of the HD gene at 4p 16.3 explains many of the puzzling 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 clinical onset of HD [1, 20-23]. 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 [24]. 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. For example, the UCHL1 gene, which encodes ubiquitin carboxyl-terminal hydrolase L1, was reported to influence age at onset of HD, with the S18Y polymorphisms accounting for 13% of the variance in age at onset in a case-and-control-study design [25]. Several previous studies have reported that a gene coding for a subunit of an ionotropic glutamate receptors (GluR6; GRIK2) acts as an HD modifier [26-28]. When analyzed in conjunction with UCHL1, 7% of the variance in the age at onset of HD could be attributed to the GRIK2 genotype variation, 13% to UCHL1, and 16% to both polymorphisms [27]. Chromosomal regions harbouring additional modifier genes have been implicated by a recent genome linkage scan (the HD-MAPS study; [29-31]. To date, the search for modifying genes has been carried out using age at onset of motor signs as the phenotypical variable under consideration, but it is clear that HD displays other phenotypic variability in disease expression, including psychiatric manifestations (e.g., depression, psychosis) and cognitive impairment (e.g., impairment of executive function and/or immediate memory). Due 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 neuroimaging abnormalities 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. REGISTRY 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. Collection of family history information and knowledge of familial relationships of REGISTRY participants will permit assessment of the variation of phenotypes within families and their degree of heritability and will be crucial for sib pair analysis. DNA samples from REGISTRY participants will permit a genome wide search for polymorphisms outside the HD gene using standard approaches (e.g. SNP maps). 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

phenotypical presentation, rate of progression and response to treatment of HD using genetic linkage and association strategies.

The clinical database on HD and the biomaterials to be collected for the REGISTRY study will be used for a variety of different analyses which may be broadly categorized as either cross-sectional analyses or longitudinal analyses. The design of REGISTRY places no limit on the sample size to be collected or a timeframe in which the study will be completed. It is intended that clinical data and biosamples will be collected until effective treatment options for HD are established. The gradual amassing of phenotypical data and biological samples will result in cumulative increases in statistical power in order to continuously improve the assessment tools that monitor the progression of HD and to detect 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).

Inclusion of a biological specimen repository in REGISTRY evolved from discussions about the current unmet needs of HD research. Advances in understanding the pathogenesis of HD and the discovery of parallel biomarkers has largely been limited by the availability of suitable collected biological specimens and the availability of prospectively collected longitudinal data. The REGISTRY biological specimen repository will provide research samples essential for current and future scientific research aimed at developing useful biomarkers of HD.

2.2. Study objectives

To collect prospective data on the phenotypical characteristics of Huntington's disease (HD) mutation carriers regardless of whether they display clinical symptoms and signs of HD and of individuals who are part of an HD family (irrespective of their mutation carrier status), in order

- to obtain natural history data on a wide spectrum of HD patients, HD mutation carriers and individuals who are part of an HD family
- to relate phenotypical characteristics
    - with genetic factors ('genetic modifiers'),
    - with data derived from the study of body fluids (blood, urine – 'wet biomarker') and
    - imaging data ('dry biomarker')
- to expedite identification and recruitment of participants for clinical trials
- to plan for future research studies (observational and interventional trials aimed at better symptom control or aimed at slowing or postponing the onset and progression of HD).

2.3. Study design

REGISTRY consists of 3 components

- a clinical phenotypical characterization
- the collection of biological specimen
- the collection of family history data

2.3.1. Clinical phenotypical characterization

The clinical phenotype will be assessed and documented based on information obtained from three sources:

- trained raters (e.g. neurologists, psychiatrists, neuropsychologists etc.) who record their clinical impression using the Unified Huntington's Disease Rating Scale (UHDRS'99) and the Hamilton Depression Rating Scale (HDRI)
- affected/HD mutation carrier/person at risk for HD themselves who self-report on their perceived quality of life (SF-36), their mood (Beck's Depression Inventory - BDI) and on the economic impact HD has on their lives (Client Services Receipt Inventory - CSRI)
- companions/carer-givers who record the impact of HD/mutation carrier status/at risk status on the families/social core units (Care Giver Questionnaire - CGQ)

The impressions of trained raters are captured using the Unified Huntington's Disease Rating Scale 99 (UHDRS'99) including a measurement of weight and height and a clinical rating scale for depression, the Hamilton Depression Inventory (HDI).

Specifically, the following information will be collected:

- Demographics (date of birth, gender, etc.)
- Medical History
- Co-morbid conditions
- HD-Mutation (CAG repeat analysis, size of the alleles, laboratory performing the analysis, date of the analysis)
- Current medication
- Weight & height (+ BMI)
- UHDRS motor assessment
- UHDRS cognitive assessment
- UHDRS functional assessment (including functional scale, independence scale and total functional capacity (TFC) scale)
- UHDRS behavioural assessment

In addition, the investigator's clinical impression regarding the presence or absence, the intensity and the frequency of symptoms and signs indicative of clinical depression is documented using a well standardized tool, the Hamilton Depression Rating Scale (HDRS).

Aside from the impression of trained observers the self-assessment of the affected/HD mutation carrier/person at risk for HD with respect to their Quality of Life (QoL) and mood is documented using standard tools (SF-36 for the measurement of QoL and the Beck's Depression inventory as a measure of depression). Lastly, the economic impact HD has is documented (Client Service Receipt Inventory - CSRI; this questionnaire is completed both by the affected/HD mutation carrier/person at risk as well as by their companions/carer-givers).

Finally, companions/carer-givers are asked to record the impact that the HD/mutation carrier status/at risk status has on the families/social core units by filling in a questionnaire (Care Giver Questionnaire).

At the baseline study visit, trained raters will administer the Unified Huntington's Disease Rating Scale 99 (UHDRS'99) and will fill in the Hamilton depression inventory. The study

participants will complete the SF-36, the BDI and the HSUI. A companion (if available) will complete the CGQ and will assist in filling in the CSRI. In addition, at the baseline visit, participants will be asked to consider the following optional study procedures:

2.3.2. Collection of biological specimen

Donation of biological specimens – 30 ml of blood and 30 ml of urine – at the baseline visit and at each annual visits. Participants will be given the option of donating blood and urine samples; the biological specimens are donated with the understanding that all specimens are used for HD related research and that they are stored at a central bio-repository.

- 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 phenotypical characteristics/presentations (e.g. the life time occurrence of psychosis). For this purpose two tubes of ACD blood are drawn for the extraction of DNA, for the generation of lymphoblastoid cell lines and for the cryopreservation of lymphocytes.
- Plasma (one tube of 10 ml containing Lithium-Heparin) for studies to establish and validate markers tracking the progressive course of HD (e.g. proteomics)
- Urine (30 ml) for studies to establish and validate markers tracking the progressive course of HD (e.g. metabolomics).

Note: the result of the genotyping by the central laboratory will be made available to the study site which sent the specimen to the bio-repository. The size of both the smaller and the larger allele will be displayed at the biosample page within the REGISTRY CRF. It is the responsibility of the study site sending in samples to ensure that no predictive testing is inadvertently performed through this procedure. To reduce the chances of an inadvertent predictive testing of participants at risk, the following procedure will be implemented: the results of the genotyping by the central laboratory will only be displayed at the biosample CRF page provided (i) the CRF page on CAG is completed OR (ii) if the diagnostic confidence level for the clinical diagnosis of HD (recorded in part III - motor assessment - of the UHDRS'99) equals 4 and if the motor score (as well recorded in part III - motor assessment - of the UHDRS'99) is ≥ 10 even in the absence of a genetic test result or if the results of genotyping by a diagnostic laboratory are unavailable. Furthermore, the study site personnel must to compare the results obtained from a certified diagnostic laboratory as recorded on the CAG page of the REGISTRY CRF with the results reported by the central laboratory affiliated with the bio-repository. In the (hopefully unlikely) occasion of discrepant results of clinical relevance (e.g. a repeat size below the 35 in an individual regarded as a symptomatic mutation carrier) a repeat test in a certified diagnostic laboratory is advised.

2.3.3. Completion of a family history questionnaire (FHQ)

All participants with a family history of HD will be invited to participate. The FHQ attempts to collect information about the history of HD within a family unit and will therefore focus on the side of the family affected by HD. Within the FHQ data on 3 generations will be assembled (data on the parents and their siblings (i.e. aunts and uncles), data on the grandparents, and data on the children of the affected and the offspring of their siblings (i.e. nieces and nephews) as well as data on the spouse. The purpose of the FHQ is (1) to render linked biosamples or data sets identifiable while protecting the privacy of all donors and (2) to obtain a family tree as an important part of standard medical care. A questionnaire will be

handed to consenting participants to share their family tree by indicating how many siblings, children and relatives up to the second degree they have and to volunteer 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 cause of death (as accurately as possible)

- opinion of the contributor as to whether 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

From these data a family tree will be generated using appropriate software. Within this family tree the symbols representing those members of the family who consented to participate in 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 everybody volunteering information by using exclusively pseudonyms in all electronic data bases.

In order to ensure an appropriate number of linked biosamples and linked clinical data sets, participants are asked (provided that the feel comfortable to do so) to forward an invitation to their relatives to consider taking part in REGISTRY.

Relatives of index participants would then be informed about REGISTRY by personnel of a study site of their choice and invited to participate in all components including the clinical data documentation, the biosample component and the family history component. Therefore family histories for a given family unit may be ascertained several times thus corroborating the accurateness of the data provided. In order to allow crosschecks of potentially conflicting information given by various members of the same family unit and to accommodate the fact that members of the same family unit may chose more than one study site to interact with, participants are informed that annotated family trees are shared within the network (i.e. are made available outside the study site the participants chose to interact with) and that annotation of family trees will be completed by central coordination/monitors.

Example: participant A chooses study site X to participate in all components of REGISTRY. As a result of participant A's contribution to the family history component, a family tree will be drawn based on the information volunteered by participant A with just one symbol annotated by a pseudonym (i.e. the symbol representing A). Since participant A felt comfortable alerting relatives to the option of participating in REGISTRY, three relatives contacted study site X and consented to REGISTRY. As a consequence, three more FHQ were filled out on the same family unit corroborating the family tree obtained through participant A and allowing the annotation of symbols representing participants B-D. In addition, a member of this family unit residing far away, participant E, chooses study site Y to

participate in REGISTRY. Based on the information volunteered by participant E, study site Y now generates a family tree (which may or may not be identical to the family tree derived from the information of participants A-D at study site X) and annotates only one symbol, the one representing participant E. Since study site Y was told by participant E that other members of the family contributed to REGISTRY at another site, study site Y alerts central coordination about this fact. Central coordination will then identify the respective family tree and will annotate the symbols representing the consenting members and will generate an entry in the family unit data base. As a result, the family tree available for study sites X and Y will now have 5 symbols annotated (previously 4 symbols annotated for study site X, 1 symbol annotated for study site Y). The clinical data on participants A-D will continue to be exclusively accessible to study site X, and the data on participant E exclusively for study site Y. On request, and if study sites concerned express this wish in writing, access to data of all members of a given family unit can be made available to all study sites involved in the care of the members of this family unit.

Authorized individuals (e.g. researchers with an EHDN approved project) will have access to the family unit database thus allowing them to explore the availability of data and biosamples to determine the feasibility of a given project and to access the appropriate data/samples.

Participants will be given the option of completing the FHQ during the study visit or can take the questionnaire (along with a stamped, addressed envelope) home to complete and mail it back to the study site. If the completed questionnaire is not received within one month of the study visit, the site will follow-up with the participant.

2.4. Observation schedules

Investigators should evaluate participants at least once a year. The study calls for the documentation of annual assessments. The predefined range of tolerance for the annual assessment is ± 1 month. If the participant has to be seen more frequently than once a year for medical reasons, assessments can be conducted and can be documented more frequently.

At each annual follow up visit, the following will take place:

A clinical phenotypical characterization as described above. As part of the UHDRS, information about events, which have occurred since the last visit (e.g. changes in occupation, concurrent health problems, changes in medication etc.) will be collected.

Participants who consented to donate biological specimens and to volunteer the family history will be requested

- to update the FHQ: he or she will be asked to provide information about new deaths and onsets of HD
- to donate a second sample of biological specimens – 30 ml of blood and 30 ml of urine – to obtain the following materials
- One tube of blood (one tube containing ACD) for the cryopreservation of lymphocytes
- Two tubes of plasma (two tubes of 10 ml each containing Lithium-Heparin) for studies to establish and validate markers tracking the progressive course of HD (e.g. proteomics, metabolomics)

- Urine (30 ml) for studies to establish and validate markers tracking the progressive course of HD (e.g. metabolomics).

Note: at the discretion of the steering committee of REGISTRY, the additives in the tubes used for blood donation as well as the procedures for shipment (ambient temperature, on dry ice etc.) may change; these changes will not be regarded as substantial changes in the study procedures, i.e. are not considered important enough to justify an amendment.

All participants will be given the opportunity to re-evaluate their decisions regarding participation in the optional components.

Study personnel will work in conjunction with the study participants to create a mechanism to best contact the participants to set up yearly study visits. This will be used to maximize participant retention in the study. Participants will be given the option of allowing study personnel to contact them in-between visits for additional clarifications or to provide updates regarding REGISTRY or to consider upcoming intervention studies for which participants in REGISTRY may be eligible.

2.6. Description of the study population

2.6.1. Participant selection criteria

Participants includes those who are willing to participate in regular (annual) evaluations conducted by the investigators and have a diagnosis of HD, are HD mutation carriers or persons at risk for HD (first and second degree relatives of people affected by HD) as well as spouses of participants to serve as controls.

2.6.2. Inclusion criteria

The following individuals may be eligible to participate

- Individuals with clinical features of HD with a confirmatory family history of HD or in the setting of DNA testing results demonstrating the presence of the HD mutation (i.e. a CAG repeat expansion within the HD gene >35 on larger allele) (category 1). A confirmatory family history of HD is defined by the presence of either a parent or sibling with clinically diagnosed features of HD or a first-degree relative known to be a carrier of the HD gene through pre-symptomatic DNA testing.
- Individuals without clinical features of HD in the setting of DNA testing result demonstrating presence of the HD mutation (i.e. CAG repeat expansion within the HD gene >35 on larger allele) (category 2)
- First-degree relatives (i.e. parents, siblings, or children) of individuals with HD (category 3)
- Second-degree relatives (i.e. grandchildren, nieces and nephews) of participating individuals with HD (category 4)
- Family members of participating individuals from category 1 or 2 who are know not to carry the HD mutation (e.g. spouses, siblings and children who underwent predictive genetic testing) (category 5)

Participants may be male or female and of any age. All participants must be able to provide consent for themselves, have a parent/guardian who can provide parental permission, or have an authorized legal representative who can provide consent.

Note on vulnerable subjects and subjects with reduced capacity for consent:
Children and mentally compromised individuals may be included in REGISTRY. Children with HD should be included in this study because REGISTRY should reflect the entire spectrum of HD including juvenile HD. Juvenile HD patients present with a clinical phenotype quite distinct from the phenotype of adult onset patients. Their incidence is approximately 10% of all affected by HD. A better description and understanding of juvenile HD patients is a prerequisite to develop treatment options for this important subpopulation. In addition, it is possible that children will be eligible because they have parents or siblings who are affected by HD. Parental permission will be obtained from one parent/guardian for each subject under the age of 18 who participates in this study. In addition, verbal or written assent by the participating child will be obtained when appropriate. Guidelines for obtaining assent are detailed below (please see the paragraph: 'Participant informed consent').

Individuals with HD whose disease has progressed to the point of mental incapacity may be enrolled in REGISTRY. Patients in very advanced stages of HD should be included in this study, because REGISTRY should ascertain the entire spectrum of HD. A study site investigator will determine mental incapacity at the baseline visit. Mentally compromised individuals will be asked to participate with the consent of an authorized legal representative.

2.6.3. Exclusion criteria

a) Participants who are unable to understand the study protocol or are unable to give informed consent, and have no legal representative
b) Participants with choreic movement disorders other than HD

2.7. Data security

Participant data are entered after creating a unique pseudonym for each participant, based on unchanging information (date of birth, birth name, place of birth and mother's maiden name). The pseudonym is a nine figure number created by a secure one-way algorithm, e.g.: Christine Mustermann, Date of Birth: 13 April 1964, Place of Birth: Berlin, Birth name: Maier; Mother´s maiden name: Schmidt. These data give the pseudonym: 344-259-192. More details are given in the data security information sheet (please see Appendix A).

The identifying data are never stored electronically. The investigator must store the original data and the pseudonym in the source documents (patient file) and in the investigator file.

2.8. Method of Identification and Recruitment of study subjects

The research staff at the site will recruit potentially eligible subjects and inquire as to their willingness to participate in this study.

2.9. Participant informed consent

The research staff at the study sites will seek consent from any eligible subject willing to participate. At the time of the potential participant's visit an explanation of the study and a copy of the Patient Information Sheet (see appendix A) prepared in the respective native language and approved by the respective IRB will be provided. The opportunity to read the consent will be given and questions answered by the research staff. The subject will be given

the opportunity to take the consent form home to discuss with family members, and consent will be obtained at a future visit. Participation in the study will not be pursued if the potential participant declares not to be contacted, unless the potential participant agrees to future discussion.

The site investigator will determine whether or not a potential participant has diminished mental capacity which may interfere with giving informed consent. If a potential participant with mental incapacity is approached for enrolment, the research staff will seek consent from that subject's legal representative. A legal representative may be defined as an individual with guardianship or a health care proxy, provided consenting for research studies is within the scope of the proxy's delegated responsibilities. Health care proxies may be the potential participant's next-of-kin, a relative, or a long-term caregiver/significant other or an appointee by a court of law; this person must be mentally cognizant and be able to understand the procedures, risks, and benefits involved with the study. At the time of the subject's visit, an explanation of the study and a copy of the consent will be provided to both the subject and the authorized representative. Opportunity to read the consent will be given and questions answered by the research staff. The subject/authorized representative will be given the opportunity to take the consent form home with them for further discussions and consent will be obtained at a future visit. Although the authorized representative will be officially providing consent for the subject to participate, the subject must also agree to participate.

Participants with HD may lose mental capacity to provide continued consent during the course of this study because of the study's long-term nature. Therefore, participants who have been diagnosed with HD will be asked to consider appointing a research proxy to aid in the decision making process for continued participation. Participants will be encouraged to discuss their future study participation wishes with the research proxy.

For potential participants who are children at the time of enrolment, parental permission will be obtained from one parent/guardian for each subject under the age of 18 who participates in this study. In addition, verbal or written assent by the participating child will be obtained when appropriate. Guidelines for obtaining assent include:

- for children under the age of 7, only written parental permission will be obtained and documented
- for children 7 to 12 years of age, written parental permission and verbal assent by the participating child will be obtained and documented.
- for children 13 to 17 years of age, parental permission with written assent by the participating child will be obtained and documented through signature.

Any subject who begins participation in this study as a minor (under the age of 18) will be asked to reconsent for this study after turning 18 years of age.

2.10. Documentation of Consent/Assent

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

2.11. Study procedures - descriptions

2.11.1. Unified Huntington's Disease Rating Scale 99 (UHDRS 99)

The Unified Huntington's Disease Rating Scale 99 (UHDRS'99) will be used by trained raters to assess and document the clinical aspects of HD. The UHDRS'99 consists of four parts: cognition, motor function, behaviour, and functional capacity.

The **motor section** of the UHDRS assesses motor features of HD using standardized ratings of oculomotor function, dysarthria, motor impersistence, chorea, dystonia, bradykinesia, gait, and postural stability. The total motor impairment score is the sum of the individual motor ratings (range 0 – 124); higher scores indicate more severe motor impairment.

Cognition is assessed by a verbal fluency test (in the form of letter fluency), Symbol Digit Modality Test and Stroop Interference Test. Higher scores indicate better cognitive performance.

The **behavioural assessment** measures frequency and severity of symptoms related to altered affect, thought content and coping styles. The total behaviour score is the sum of all responses; higher scores indicate more severe impairment.

Functional assessments include the total functional capacity (TFC), the independence scale, and a checklist of common daily tasks; higher scores indicate better functioning. The extent of functional disability correlates well with the extent of basal ganglia degeneration detected by neuroimaging.

The total UHDRS 99 takes approximately 45 minutes to complete. To maintain consistency of the data collected for REGISTRY, at each study site the assessment should be performed by the same individual(s) at each visit.

2.11.2 Family History Questionnaire (FHQ)

A questionnaire will be handed to consenting participants to share their family tree by indicating how many siblings, children and relatives up to the second degree they got and to volunteer 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

From these data a family tree will be generated using appropriate software. Within this family tree the symbols representing those members of the family who consented to participate in 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 whilst also protecting the privacy of individuals volunteering information through the use of their pseudonyms.

In order to ensure an appropriate number of linked biosamples and linked clinical data sets, participants are asked (provided that the feel comfortable to do so) to forward an invitation to their relatives to consider taking part in REGISTRY.

Relatives of index participants would then be informed about REGISTRY by personnel of a study site of their choice and invited to participate in all components including the clinical data documentation, the biosample component and the family history component.

2.11.3. CAG Genotyping

If the participant agrees to participate in the CAG genotyping, blood (10 ml) will be drawn one time during the study. This portion of the study is optional. The participant may choose to participate at the baseline visit or at any of the subsequent yearly visits. CAG genotyping will be performed to detect the length of the CAG repeat expansion in the HD gene. BioRep will process blood for DNA extraction and genotyping.

CAG genotyping is performed by BioRep according to the following procedures:

- One tube of peripheral blood will be collected in a 10 ml yellow topped ACD (acid citrate dextrose solution A) tube and shipped by a fast courier service.
- BioRep will assign a unique identifier to the sample.
- DNA will be obtained from the blood using standard procedures.
- Routine quality control studies will be conducted to estimate the quality and integrity of the DNA.
- Genotyping will be performed according to standard procedures using two sets of primer pairs [32-34].
- All activities and testing will be documented.

2.11.4. Specimen Repository: BioRep in Milano (Italy)

If the participant agrees to donate biosamples for research into genetic modifiers and into establishing biomarkers to track the progressive course of HD and for storage in a central specimen repository, blood (30 ml) and urine (30 ml) will be collected at each visit. This component of the study is optional. The participant may choose to participate at the baseline visit or at any of the subsequent annual follow up visits. A portion of the blood will be used to generate lymphoblastoid cell lines, which will serve as an inexhaustible resource for future research into genetic modifiers of HD. Another portion of the blood will be processed to remove the lymphocytes and plasma. Lymphocytes will be cryopreserved and stored as backup in case cell lines fail, and in order to use them for functional as well as RNA and protein studies.

The following process will be performed for the creation of lymphoblastoid cell lines:

- One tube of peripheral blood will be collected in a 10 ml yellow topped ACD (acid citrate dextrose solution A) tube and shipped by a courier service.
- BioRep will assign a unique identifier to the sample.
- 0.5 ml of blood will be retained as a quality control specimen for identity testing

- Lymphoblastoid cell lines will be created including appropriate testing for viability and contamination.
- All activities and testing will be documented.

The following process will be performed for the isolation of lymphocytes and plasma from the blood sample:

- One tube of peripheral blood will be collected in a 10 ml yellow topped ACD (acid citrate dextrose solution A) tube and shipped by a courier service.
- BioRep will assign a unique identifier to the sample.
- 0.5 ml of blood will be retained as a quality control specimen for identity testing
- Lymphocytes and plasma will be isolated from the blood sample and cryopreserved.
- All activities and testing will be documented.

Genotypic Evaluation – To ensure uniformity of CAG repeat sizing participants in REGISTRY are asked for their permission for repeat genotyping of the mutant and normal HD alleles. The results of this genotyping will be used for research purposes only.

Urine - If the participant consents, urine (30 ml) will be collected at all visits and stored at BioRep. For additional information, see the Repository Description by BioRep.

2.12. Costs to the Participant

Participants will incur no cost for participation in this study. The participant or the participant's insurance will be responsible for the cost of all procedures associated with standard of care. Participants will receive no payment for participation in this study but may on request receive compensation for their travel expenses.

2.13. Participant risk

Since Registry is an observational study, participants do not undergo specific risks by participating. Therefore no medical insurance is provided. Participants may experience anxiety or psychological discomfort while completing the UHDRS'99 and/or the family history questionnaire. In addition, despite best efforts, it is not humanly possible to exclude with 100% certainty a breach of confidentiality by unauthorized people getting access to information in medical files and records thus resulting in a loss of confidentiality. However, all reasonable safeguards to prevent an incidence like that were undertaken. For instance, all data entered into the electronic data base of REGISTRY are stored under a code (or 'pseudonym' - a 3 x 3 number like 346-599-321 - see also data protection leaflet) instead of the name or other identifying data. Therefore at all times only the study site chosen by the participants for inclusion into REGISTRY is aware of the identifying data (e.g. name, date of birth, address) associated with the pseudonym. All users of the EHDN database outside the study site chosen by the participant EXCLUSIVELY work exclusively with coded ('pseudonymised') data. For the protection of the EHDN data base containing these pseudonymised data against unauthorised access, EHDN has several precautions in place to maintain integrity, confidentiality and security of the database. The EHDN servers are managed by full-time system administrators. All network traffic is encrypted via network hubs to minimize 'eavesdropping' attacks using SSL/TLS with a key length of 128 or more. All PC's run virus protection software full-time and are updated with the latest virus detection strings regularly. 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 study data is 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 that is also locked - different keys are required for both the computer room and the suite. The Computer room is temperature controlled. It is also 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 24 hours the system is backup to DLT tape. In addition, the data base is mirrored by a second sever in a similarly protected environment located at a physically distant (> 50 km) site. All CRF data and other critical study data are fully audit trail enabled so that all changes to the data can be monitored and/or recovered. WEBSPIRIT implements a permission-based security methodology that limits access to study data based on the particular study, user ID, and group ID. Permissions are carefully maintained to allow only the required level of access to study data. The operating environment requires username/password authentication, and implements its own permissions structure at the file system level based on user ID and group ID. Files and directories are carefully set with only the required level of access. User ID's are required to change password on a regular basis. Every precaution has been taken to assure that computer confidentiality is maintained.

For participants consenting to donate biosamples there are some additional potential risks associated with blood draw. The collection of blood specimens may cause pain and/or 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 will draw the blood for this study. In order to ensure the confidentiality of donors contributing to the central biorepository, BioRep, will BioRep 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.

2.14. 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 lead to potential treatments and to plan future research studies of experimental drugs aimed at slowing disease progression or postponing the onset of HD.

2.15. Alternatives to Participation

The only alternative to participation in this study is not to participate. The participant can choose not to take part in the optional components of the study.

2.16. Withdrawal from Participation

If a participant does not want to continue, the participant can at every time leave the study. 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. Similarly, on the participant's request all biosamples collected and stored at the central biorepository will be

destroyed. Participants have to be aware that The 'End of Study form' must be completed by the investigator, detailing the reasons for withdrawal (eg. marking "patient request").

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

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

If the participant is withdrawn by the investigator the 'End of Study form' must also be completed.

2.17. End of study/withdrawals

There is no fixed end of study. After patient death the 'Death Report form' (study form) must be completed by the investigator. If a participant does not want to continue, the participant can at every time leave the study. In addition, participants may be withdrawn from the study for the reasons listed above. In these instances, an 'End of Study form' must be completed by the investigator, detailing the reasons for withdrawal (e.g. 'patient request').

2.18. Statistical Considerations

As HD is a relatively rare disease, no single study site is in the position to obtain single-handed phenotypical (clinical) data or biosamples in sufficient numbers to conduct conclusive studies concerning the majority of questions of clinical relevance in HD. Therefore a cooperative effort appears an appealing avenue to provide large enough clinical data sets and sufficient numbers of biosamples to answer questions conclusively by conducting well powered studies. Obviously, the numbers need to answer scientific questions conclusively will depend on the outcomes and read-outs under consideration. For example, performing a meaningful factorial analysis to improve and condense clinical rating scales may require several hundred clinical data sets with a wide spread of phenotypical presentations. A genome-wide search for genetic modifiers may well require – given present days technologies – more than 3000 samples for an informative study, depending – among other factors - on the degree of heritability of the trait under consideration, the extent of genetic heterogeneity in the samples, and the density of the molecular markers being tested. At the other extreme of the spectrum, a carefully selected, small (e.g. n = 60) sample representing all clinical stages of HD may well be sufficient to strongly suggest the usefulness of a read-out from plasma as a biomarker tracking the progressive course of HD. In the future, the availability of prospectively ascertained biosamples linked to phenotypical states at the time of sample collection will permit robust conclusions about the validity of suggested biomarkers within a short time frame. Overall, data from REGISTRY should assist in determining the robustness of conclusions derived from previous studies conducted on small sample sizes using independent data sets. As a result of these considerations, each project proposal defining a specific-read out or endpoint will included a sample size calculation and – if appropriate – a power analysis specific to the objectives of this study.

As an example one may consider a sample size calculation for studies aiming to identify genetic determinants of certain characteristics of the disease phenotype (e.g. the life time occurrence of a major psychosis in HD patients). First, it is essential to estimate what fraction of the phenotypic variation is due to genetic factors. A commonly employed design to perform such an analysis is the collection of sibling pairs with the goal of estimating the heritability of the phenotype of interest. The REGISTRY sample will strive to recruit multiple members from a given family and through the collection of family history information, will be able to establish the biological relationship among individuals and use this information for

genetic analyses. Siblings are typically employed for heritability studies since they are closely related and are expected to share, on average, half their genetic material. Studies in REGISTRY will focus on estimating the heritability of a number of different quantitative phenotypes including the age of onset of disease and the rate of disease progression (as measured by a number of different parameters). For those phenotypes and traits which are heritable, the collection of DNA and of family data will allow studies to identify the genes and polymorphisms contributing to trait variability. Broad-sense heritability (H2) is estimated as twice the sibling intraclass correlation, according to the method of Falconer (1989). This implies for a phenotypic trait with 50% heritability (i.e. half the phenotypic variation is due to genetic effects), a sample of approximately 100 sibling pairs will have 80%> power (with alpha=0.05). As the genetic contribution to the trait decreases, the required sample size increases. For a trait with only 20% heritability, a sample of approximately 600 sibling pairs is required for 80% power. In addition, it is essential to perform alternate analyses such as family based association analyses. This type of analysis can be relatively inefficient in its use of family resources, but is particularly resistant to possible sources of data bias such as sample stratification.

2.19. Data Analysis

Data analysis is performed by investigators with approved EHDN proposals. Statistical and analytical methods have to be defined as part of the proposals and are ultimately the responsibility of the proposers. However, guidance from biostatisticians associated with EHDN can be provided on request and is facilitated through central coordination of EHDN.

2.20. Monitoring trial progress

For data control there will be continuous evaluation of data for plausibility. There will be additional on-site monitoring to check source documents and data entry. During the site visits, the study monitor should review original patient records and compare them with the electronic CRF. The investigator should allocate adequate time for these visits and should ensure that the monitor is given direct access to the patient source documents (e.g. hospital files). Between on-site monitoring visits the monitor should regularly check the electronic data for completeness and plausibility of the data. Missing data will be marked.

2.21. Forms and data handling

A complete CRF is attached in the Appendix. The data are entered electronically via internet-based technology. The EHDN web-portal is separated into several parts with different access rules. Any given site investigator in REGISTRY is allowed to see only data on participants under the care of the study site to which the site investigator is affiliated. Central Coordination is allowed to view all data of all centres for plausibility checks, quality control and monitoring. As detailed in the data access policy of EHDN, investigators whose projects were approved by the scientific review committee of EHDN receive a recoded, pertinent extract out of the data base. By order of the steering committee of REGISTRY, Central Coordination is permitted to statistically evaluate the whole data set. The whole database is saved on a server.

2.22. 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 Euro-

HD Network, the investigators and the IRB will agree upon such amendments prior to implementation.

2.23. Administrative responsibilities

The Investigator is responsible for the adequate medical care of the participant during the study. The Investigator must follow GCP Guidelines 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 REGISTRY trial coordination including the sponsors; the contract will be signed between authorized representatives of the respective institutions with which the investigators are affiliated and REGISTRY trial coordination represented for the time being by the University Hospital of Ulm University.

Sponsor of the REGISTRY study is the Euro-HD network in conjunction with High-Q Foundation/HP Therapeutics Foundation, Inc.

The steering committee of REGISTRY is responsible for overseeing the monitoring and data quality control procedures. Central Coordination of EHDN is responsible for the execution of monitoring according to the principles of Good Clinical Practice (GCP) and for supplying trained personal for this purpose.

The steering committee of REGISTRY is responsible for promoting inclusion into REGISTRY and for developing the protocol of the REGISTRY study further (e.g. by considering additional components like MRI imaging) and by making decisions on the biosamples collected in future follow up visits.

Access to the clinical database and to the biosamples is regulated by the policies of EHDN (see appendix). In brief, researchers interested in obtaining biosamples for further analysis have to submit brief outlines of their HD related research project to the Scientific Review Board of EHDN. The Scientific Review Board will assess whether the proposed project falls within the subject area to which participants gave their informed consent (i.e. studies to identify genetic modifiers of HD and to establish and validate biological markers for HD) and whether the proposal is ethically and scientifically sound. Once a project is approved by the Scientific Review Board, the proposer has to confirm in writing to comply with the data access and publication policy of EHDN and will provide a short abstract on the approved proposal for display at the EHDN web portal. Researchers conducting an approved project will then be granted access to explore a recoded excerpt of the clinical database of EHDN for selection of appropriate samples based on phenotypical characteristics as well as BioRep's database to explore availability of samples. The database to which the researches conducting an approved project is granted access is recoded in order to (1) control for double publication of the same data sets and (2) to avoid that researchers recognize data sets as their own contribution. In parallel and prior to the release of samples confirmation is sought from the respective leading national ERB that no objections are raised against the assessment by the Scientific Review Board of EHDN that the proposed research project falls within the subject area to which participants gave their informed consent.

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Appendices

A Information and Consent Forms

Participant Model Information Form

Name of study: REGISTRY – an observational study of the European Huntington-Disease Network (EHDN)

Dear Participant,

You are either suffering from Huntington's disease (HD), belong to a family at risk for HD, or are a relative of a patient with HD. The clinician treating you or your relative has asked you whether you are willing to participate in a study ('REGISTRY') conducted at many centres throughout Europe striving to understand HD better and to improve the currently available tools to follow the course of the disease. In addition, REGISTRY aims to help in understanding which gene(s) other than the HD mutation within the HD gene influence the presentation and the rate of progression of HD (e.g. at what age mutation carriers develop signs and symptoms). Finally, REGISTRY wants to facilitate and expedite future studies in HD by assisting e.g. in the recruitment of participants across Europe; this will enable you to enrol in studies relating to the natural progression of HD and in so called interventional studies ('drug trials') aimed at delaying disease progression or focused on ameliorating defined complaints (e.g. apathy, irritability). Therefore, it is important that you are interviewed and examined by experienced clinicians in order to record how much, or how little, you are affected or impaired by HD.

In other words: at each study visit, your physical and mental ability will be assessed; these examinations are no different from those you are already familiar with from previous consultations. In addition, you will be asked to complete questionnaires assessing your wellbeing. Lastly, your companion or other individuals involved in your care (provided you require any due to HD) will be asked to complete questionnaires to understand the caregiver burden and the possible economic consequences of HD for you, your family and your health care provider.

The results of these examinations will be entered onto an electronic database. Your name, address or any other information which could allow personal identification will never be recorded in the database. Your data will be 'pseudonymised', i.e. recorded under a 'code name' (or 'pseudonym'), which is a series of 9 digits. Therefore, nobody but the team of physicians and health care workers you choose to interact with and who provides you with this information about REGISTRY knows your identity and can trace your 'pseudonym' or code name back to your real name and other information which might identify you like date of birth or address (for details please see 'Information regarding data processing, data protection and data safety' below for issues relating to data security, including restriction of data access to authorised persons and secure transmission of data). Data entry and the use of the REGISTRY database will be carried out using the internet.

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. As a result, none of your personal data will ever be made public.

REGISTRY is a study conducted by the European Huntington's Disease Network (EHDN). EHDN is a scientific network of physicians and scientist committed to HD; The aim of the network is to carry out clinical research into HD, to improve knowledge of the natural course of the disease, and (ultimately) to find a cure for HD. EHDN is supported by an American charity, the High-Q Foundation.

There are no specific risks arising from your participation in the study given that it is an observational study. If you are willing to participate it is important that you (and a person accompanying you) attend a follow-up examination at least once a year.

We would like to ask you to consider

- your consent to a thorough standard examination and the documentation of the data obtained during your clinical examination in an electronic data base and
- your consent to yearly follow up visits;

Any additional research components described below are optional and require your explicit consent by checking the box 'YES' in the consent form. The optional components are

- a permission to be contacted in-between visits,
- the donation of blood and urine for studies to identify genetic modifiers of HD and to establish and validate biological markers for HD,
- the analysis of a blood sample for the HD mutation and
- the completion of a family history questionnaire.

You may chose to participate in all, in none or in selected optional components.

Optional component 1: permission to be contacted in-between visits
We ask you for your permission to be contacted in-between visits, because we would like to have the option

- to clarify questions with you (e.g. concerning your answers in REGISTRY questionnaires),
- to provide you with updates on REGISTRY or
- to inform you about upcoming treatment trials for which you would be eligible and in which you may want to consider your participation.

Optional component 2: Donation of blood and urine for studies to identify genetic modifiers of HD and treatment responses in HD and to establish and validate biological markers for HD
We ask you to consider donating blood to allow scientific studies to find genes which influence the features and the course of HD. The way HD presents differ quite a lot from individual to individual; an important part of this variation is caused by genes other than the HD gene. Similarly, the rate of progression of the disease differs from family to

family. Knowing about these so called genetic modifiers is important since genes which influence HD may be useful therapeutic targets and may be very helpful understanding differences between HD patients thus improving the understanding of the outcome of clinical studies and treatment trials. For this purpose we ask you to donate blood once for the generation of cell lines from blood cells which will ensure that sufficient DNA is available to carry out these studies.

In addition, we ask you to consider donating blood and urine to allow scientific studies to find markers which reflect the severity of the disease. These so called biomarkers are already well established for e.g. liver disorders: your doctor can tell by a simple blood test, how your liver is doing. It is important to find out whether similar test can be found for HD patients and how well changes in markers in blood or urine will track the progressive course of HD. Validated biomarkers are expected to allow to show the efficacy of treatments faster and with fewer participants in clinical trials compared to standard clinical rating scales to measure the progression of HD. For this purpose we ask you to donate blood and urine every year for at least 5 years. Sampling of blood and urine is required every year since finding out how much markers change over the years is critical.

In order to obtain valid results as fast as humanly possible, biosamples should be stored very safely and distributed to capable researchers in a safe and controlled way. Therefore all biosamples are stored centrally in an institution devoted to the safe storage and handling of biomaterials, BioRep in Milano, Italy. Access to biosamples will be granted to researchers whose proposals were approved by a panel of experienced scientists and clinicians who form the Scientific Review Committee of EHDN and whose proposals were judged to be well within the subject area for which you gave informed consent, i.e. represent studies into genetic modifiers and biological markers for HD.

Optional component 3: Analysis of a blood sample for the HD mutation
We ask you for your permission to consider to allow us to measure the number of CAG repeats in the HD gene. This examination will allow everybody to be very certain about the HD mutation and the precise length of the CAG repeat. Given the importance of the HD mutation it is felt to be of advantage to have the results of more than one analysis based on an independently obtained sample.

The collection of blood may cause pain and/or bruising at the site where blood is drawn. Fainting or feeling light-headed may occur during or shortly after having blood drawn. If you experiences this, you will be instructed to lie down immediately to avoid possible injuries. Localized clot formation and infections may occur, but this is very rare. The amount of blood collected is small (30ml) and the interval between collections is long, so there is no risk of developing an anemia.

Optional component 4: Family History Questionnaire
We ask you to consider answering some questions regarding your family history. HD is an inherited disease and it is part of standard medical care to obtain a family tree. Most importantly, with the help of the family history questionnaire as designed for REGISTRY

one can recognize whether biosamples or clinical data sets are linked and therefore apply the very powerful technique of sib-pair analysis while protecting the privacy of all donors. Participants are asked to list, how many siblings, children and relatives up to the second degree they have and to volunteer non-identifying information such as gender and year of birth and whether their relatives are still alive or already dead and an opinion whether a member of a family is affected with HD or carries the HD mutation. The identity of the participants and of all further donors of biosamples is protected by the exclusive use of code names ('pseudonyms') for all donors. In addition, participants are asked whether they feel comfortable to forward an invitation to their relatives to consider taking part in REGISTRY.

VOLUNTEERING
Your participation in this research project is voluntary. You are free to withdraw from the study at any time and without giving reason. This potential withdrawal does not affect your continuing medical treatment.

INSURANCE
Because the Registry is neither a pharmacological study nor a study to test new diagnostic procedures, there are no additional health risks and the participants therefore do not need insurance.

CLINICIAN CONTACT
Should you have any questions at anytime during the course of the research project you can reach *(local investigators)* on telephone number *(telephone number of local investigator)* at any time during working hours. For emergencies out of hours, ring *(local emergency number)*.

CONFIDENTIALITY/DATA PROTECTION:
All clinicians and related medical staff involved in looking after you during this clinical study are bound 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 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.

Place, date Name of the consenting clinician

EURO-HD-Network: Information regarding data processing, data protection and data security.

An essential safety aspect of the project is the processing of my data in an exclusively 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 name ('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:
Maria, Miller nee Mustermann, born 10.11.1964 in Ulm, mother's maiden name Schmidt. This information results in the code name ('pseudonym') 425-491-326.

Importantly, the pseudonym is created on the basis of a so-called 'secure hash-algorithm'. By this mathematical operation a unique value is assigned during a complicated, one-way procedure. The mathematical algorithm used ensures that nobody (not even the system programmer) can reconstruct from the result (the 'pseudonym') the information which was used to generate the pseudonym (i.e. your unique personal data) in the first place.

The personal data transmitted to generate the pseudonym are held only for the calculation of your code name ('pseudonym') in the working memory of a large computer ('server'). The calculation of the pseudonym requires a very short time (milliseconds). Viewing personal data during this time is impossible. Thereafter 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 data base entries and every use of data is exclusively carried out under the assigned pseudonym.

Which data do I have to disclose apart from the data required to create my pseudonym in the course of the REGISTRY study and subsequent studies?

During the course of the REGISTRY study, some health and/or medical data will be recorded (see Participant Information Sheet for further details). If you are participating in any subsequent studies, your clinician will give you detailed information about the study and the data required for it accordingly. Each subsequent study requires separate participant consent.

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 terminology to you and to answer questions you may have.
2. The clinician treating you: The study site team enrolling you for REGISTRY is the only one apart from yourself who can link your pseudonym to your identifying data (i.e. name, address etc.). After generation of the pseudonym all entry of clinical information in the data base is carried out under your code name ('pseudonym'). Your study site team including your treating clinician can view all clinical data recorded under pseudonym.

3. EURO-HD staff: EURO-HD staff can view the data stored under your pseudonym in order to ensure correct documentation and high data quality to contact the study site team for clarifying questions. EURO-HD staff can only view and use pseudonymised data entered on the EURO-HD network. For the purpose of data control, staff of the EURO-HD-Network ('monitors' and 'auditors') are allowed to check with your study site team that the data entered onto the network matches with the data found in your medical records. Monitors/ auditors are bound by medical confidentiality.
4. Authorized researchers (scientist/clinicians): Scientists/clinicians who are involved in HD research can apply to the scientific review board of EHDN (a group of experienced clinicians and scientists) for authorisation to obtain access to the data base. Authorized researchers can only view coded data. To ensure the highest degree of confidentiality pseudonyms are recoded before the data bank is made available to authorized researchers. Thereby it is guaranteed that all publications reporting on the findings of authorized research exclusively use anonymised data report format (i.e. not even using the pseudonym).
5. System administrators: In order to safeguard the EURO-HD-Network central database, a small number of authorised system administrators can view pseudonymised data.
6. Other groups and individuals: No-one other than the groups and individuals described above can gain access to or receive the data stored about you.

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. This implies for all practical purposes that 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 code name ('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. A complete deletion of data is difficult, since data are likely to have become part of scientific studies and therefore need to be kept on record in compliance to laws and regulations to allow future cross checks and data verifications, even years after the research was completed. However, all links to you can be deleted and irreversibly destroyed. As a result, thus not even the physicians chosen by you for enrolment into REGISTRY will any longer be able to recognize data as data belonging to you. Such a complete anonymisation will be carried out in the following cases:

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

Location, date Name of the consenting clinician

Participant Model Consent Form

REGISTRY – an observational study of the European Huntington-Disease Network (EHDN)

Content, procedures, risks and aims of the research project named above as well as the right to view the data recorded was explained to me in detail by Dr ……..……..……..……..
I had the opportunity to ask questions and obtained answer which I felt were satisfactory. I had sufficient time to decide whether or not I want to participate in the project. I received a copy of the patient information and of the consent form.

Please check Yes or No for each question below, referring to the following optional study procedures:

Contact in-between study visits
I give my permission for my study site team to contact me in-between visits
to clarify questions (e.g. concerning my answers in REGISTRY questionnaires),
to provide me with updates on REGISTRY or
to inform me about upcoming treatment trials for which I would be eligible and in which I may want to consider participation.

□ Yes □ No

Donation of blood and urine for studies to identify genetic modifiers of HD and to establish and validate biological markers for HD
I give my permission for the collection of blood (30 ml or 3 tubes each containing two teaspoons) and urine (30 ml) from me and declare to donate them for studies to identify genetic modifiers of HD and to establish and validate biological markers for HD. I understand that my samples are submitted to and stored at a central biorepository located in Milano (Italy) 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.

□ Yes □ No

Family History Questionnaire
I agree to participate in the collection of family history information. I understand that in addition I am offered information sheets on REGISTRY to allow me to inform my relatives about this option; I am under no obligation to distribute them if I don't feel comfortable with it.

□ Yes □ No

Analysis of a blood sample for the HD mutation
I give my permission for a CAG analysis on my DNA; these results are for research only.

□ Yes □ No

Information and consent form regarding data protection

During scientific studies, personal data and medical findings about you are recorded. The storage, analysis and communication of data relating to the study are carried out according to legal requirements and entail the following consent before participating in the study.

1. I agree that data/medical data obtained during the course of this study can be recorded in questionnaires and on electronic data carriers and processed without providing personal identity. All pseudonymised data are stored at a server located at the University of Ulm, Germany. In addition, some selected data (pseudonym, age, sex and disease state-whether one represents a control or HD mutation carrier) will be stored at the server of the central biorepository in Milano, where the biological samples are stored.
2. I also agree that authorised persons who are bound by confidentiality (e.g. from the sponsor, or the University) 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.

Name of the Participant
……

Signature of the participant
……

Place, date……

Participant Information (Companions)

Name of study: REGISTRY – an observational study of the European Huntington-Disease Network (EHDN)

Dear Companion,

You are accompanying/assisting somebody affected by Huntington's Disease (HD). Your affected partner/relative/friend takes part in a research project conducted at many centres throughout Europe (REGISTRY) striving to understand HD better and to improve the currently available tools to follow the course of the disease.

Since awareness of the symptoms and signs of HD may differ between affected and their companions, and given the fact that an illness of a close one has an impact on your own life, we would like to ask you to complete a questionnaire at each annual visit. This questionnaire inquires about the impact of the illness of your companion on you. If you decide to take part in this project it would be important to join your companion at least once a year for the follow-up visit.

The results of your companion's examinations will be saved in an electronic database by the medical staff interviewing and examining you, obviously without saving name, address or other data that would allow the identification of your companion. The questionnaire that you fill in will be handled likewise.

The European Huntington's Disease Network (Euro-HD Network) is a network supported by an American foundation, the High-Q Foundation. The aim of the network is to carry out clinical research into HD and to facilitate and to expedite the performance of future (treatment) trials. Your consent solely relates to the electronic registration of your statements in the questionnaire. Data entry and the use of the database, which is held at the project's Central Coordination in Ulm, Germany, is carried out using the internet.

How it is ensured that only authorised people have access to the data, and how it is provided that through the communication via the internet the data protection does not get hurt, please read "Information regarding data processing, data protection and data security".

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

Volunteering

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

Contact

Should you have any questions at anytime during the course of the research project you can reach *(local investigators)* on telephone number *(telephone number of local investigator)* at any time during working hours. For emergencies out of hours, ring *(local emergency number)*.

Confidentiality/data protection

All clinicians and related medical staff involved in looking after you during this clinical study are bound 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 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.

EURO-HD-Network: Information regarding data processing, data protection and data security.

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

Your companion's clinician will enter certain data about him/her into the computer. From these personal data a unique code name ('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:
Maria, Miller nee Mustermann, born 10.11.1964 in Ulm, mother's maiden name Schmidt. This information results in the code name ('pseudonym') 425-491-326.

Importantly, the pseudonym is created on the basis of a so-called 'secure hash-algorithm'. By this mathematical operation a unique value is assigned during a complicated, one-way procedure. The mathematical algorithm used ensures that nobody (not even the system programmer) can reconstruct from the result (the 'pseudonym') the information which was used to generate the pseudonym (i.e. the unique personal data of your companion) in the first place.

The personal data transmitted to generate the pseudonym are held only for the calculation of your code name ('pseudonym') in the working memory of a large computer ('server'). The calculation of the pseudonym requires a very short time (milliseconds). Viewing personal data during this time is impossible. Thereafter 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 data base entries and every use of data is exclusively carried out under the assigned pseudonym.

Which data do I have to disclose in the course of the REGISTRY study?

During the course of the REGISTRY study, you will be asked about the impact of your companion's disease on you. Your statements will be related to all other medical data of your companion.

Who can see and use my data?

1. The clinician treating your companion
The study site team enrolling your companion for REGISTRY is the only one who can link your data. All entry of clinical information in the data base is carried out under your companion's code name ('pseudonym'). The study site team including the treating clinician can view all clinical data recorded under the pseudonym.
2. EURO-HD staff: EURO-HD staff can view the data stored under your companion's pseudonym in order to ensure correct documentation and to rectify transcription errors by contacting the study site team for clarifying questions. EURO-HD staff can only view and use pseudonymised data entered on the EURO-HD network. For the purpose of data control, staff of the EURO-HD-Network ('monitors' and 'auditors') are allowed to check with the study

site team that the data entered onto the network matches with the data found in the medical records. Monitors/ auditors are bound by medical confidentiality.
3. Authorized researchers (scientist/clinicians): Scientists/clinicians who are involved in HD research can apply to the scientific review board of EHDN (a group of experienced clinicians and scientists) for authorisation to obtain access to the data base. Authorized researchers can only view coded data. To ensure the highest degree of confidentiality pseudonyms are recoded before the data bank is made available to authorized researchers. Thereby it is guaranteed that all publications reporting on the findings of authorized research exclusively use anonymised data report format (i.e. not even using the pseudonym).
4. System administrators: In order to safeguard the EURO-HD-Network central database, a small number of authorised system administrators can view pseudonymised data.
5. Other groups and individuals: No-one other than the groups and individuals described above can gain access to or receive the data stored about you.

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

All data travelling via the internet are encrypted. This implies for all practical purposes that 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 code name ('pseudonym').

How long is my and my companion's 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. A complete deletion of data is difficult, since data are likely to have become part of scientific studies and therefore need to be kept on record in compliance to laws and regulations to allow future cross checks and data verifications, even years after the research was completed. However, all links to you and your companion can be deleted and irreversibly destroyed. As a result, not even the treating physicians will any longer be able to recognize data as data belonging to you or your companion. Such a complete anonymisation will be carried out in the following cases:

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

Location, date Name of the consenting clinician

Consent Form (Companions)

Name of study: REGISTRY – an observational study of the European Huntington-Disease Network (EHDN)

Content, procedures, risks and aims of the research project named above as well as the right to view the data recorded has been explained to me in sufficient detail by Dr… …..

I have had the opportunity to ask questions and have received answers to them.

I have had sufficient time to decide whether to participate in the project.

I have received a copy of the participant information (companions) and consent form (companions).

- **Information and consent form regarding Data Protection**

During scientific studies, personal data and medical findings about you are recorded. The storage, analysis and communication of data relating to the study are carried out according to legal requirements and entail the following consent before participating in the study:

1. I agree that data /medical data taken during the course of this study can be recorded in questionnaires and on electronic data carriers and processed without providing personal identity.

2. I also agree that an authorised person who is bound by confidentiality (e.g. from the sponsor, or the University) can view the personal data recorded as far as it is necessary for data control of the project. For this aim, I release the clinician from the requirement for medical confidentiality.

Name of the Participant

……

Place, date……

Signature of the participant

Participant Information (Control person)

Name of study: REGISTRY – an observational study of the European Huntington-Disease Network (EHDN)

Dear Participant,

You are a companion of a person affected by Huntington's Disease (HD). Your companion takes part in a research project conducted at many centres throughout Europe (REGISTRY) striving to understand HD better and to improve the currently available tools to follow the course of the disease.

You can help in finding new and improved tools to follow the course of HD by consenting to donate a small amount of your blood (20 ml = 4 teaspoons) and a small amount of urine (30 ml). To make sure that your own state of health (specially if you are suffering from a chronic disease) can be considered when examining blood and urine samples donated by you as control, ,we ask you to agree to an interview about your state of health and a short physical examination.

The results of your interview and of your physical examination will be saved – like those of your spouse/relative/friend affected by HD - in an electronic database by the medical staff interviewing and examining you, obviously without saving name, address or other data that would allow your (or your companions) identification.

We ask you for your permission for:

- a short, standard interview and examination and the documentation of the data obtained during your clinical examination in an electronic data base and
- donation of blood and urine as a control group for blood and urine samples of affected persons

We have asked your affected companion to consider donating blood to allow scientific studies to find genes which influence the features and the course of HD. Knowing about these so called genetic modifiers is important since genes which influence HD may be useful for therapeutic targets and may be very helpful understanding differences between HD patients thus improving the understanding of the outcome of clinical studies and treatment trials. Blood samples of people who do not carry the HD mutation and who do not suffer from neurological or psychiatric disorders are essential for comparison. For this reason we ask you to donate blood once for the generation of cell lines from blood cells which will ensure that sufficient DNA is available to carry out these studies.

In addition, we ask you to consider donating blood and urine to allow scientific studies to find markers which reflect the severity of the disease. These so called biomarkers are already well established for e.g. liver disorders: your doctor can tell by a simple blood test, how your liver is doing. It is important to find out whether similar test can be found for HD patients and how well changes in markers in blood or urine will track the progressive course of HD. Validated biomarkers are expected to allow to show the efficacy of treatments faster and with fewer participants in clinical trials compared to standard clinical rating scales to measure the progression of HD. As for studies into genetic modifiers, a comparison with blood samples of people who do not carry the HD mutation and who do not suffer from neurological or psychiatric disorders is indispensable.

In order to obtain valid results as fast as humanly possible, biosamples should be stored very safely and distributed to capable researchers in a safe and controlled way. Therefore all

biosamples are stored centrally in an institution devoted to the safe storage and handling of biomaterials, BioRep in Milano, Italy. Access to biosamples will be granted to researchers whose proposals were approved by a panel of experienced scientists and clinicians who form the Scientific Review Committee of EHDN and whose proposals were judged to be well within the subject area for which you gave informed consent, i.e. represent studies into genetic modifiers and biological markers for HD.

The collection of blood may cause pain and/or bruising at the site where blood is drawn. Fainting or feeling light-headed may occur during or shortly after having blood drawn. If you experiences this, you will be instructed to lie down immediately to avoid possible injuries. Localized clot formation and infections may occur, but this is very rare. The amount of blood collected is small (20ml) and the interval between collections is long, so there is no risk of developing an anaemia.

The European Huntington's Disease Network (Euro-HD Network) is a network supported by an American foundation. The aim of the network is to carry out clinical research into HD and to facilitate and to expedite the performance of future (treatment) trials. Data entry and the use of the database, which is held at the project's Central Coordination in Ulm, Germany, is carried out using the internet.

To understand how it is ensured that only authorised people have access to the data, and how safe communication via the internet is achieved, please read the paragraph below entitled "Information regarding data processing, data protection and data security".

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

Volunteering

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

Contact

Should you have any questions at anytime during the course of the research project you can reach *(local investigators)* on telephone number *(telephone number of local investigator)* at any time during working hours. For emergencies out of hours, ring *(local emergency number)*.

Confidentiality/data protection

All clinicians and related medical staff involved in looking after you during this clinical study are bound 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 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.

EURO-HD-Network: Information regarding data processing, data protection and data security.

An essential safety aspect of the project is the processing of my data in an exclusively 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 name ('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:
Maria, Miller nee Mustermann, born 10.11.1964 in Ulm, mother's maiden name Schmidt. This information results in the code name ('pseudonym') 425-491-326.

Importantly, the pseudonym is created on the basis of a so-called 'secure hash-algorithm'. By this mathematical operation a unique value is assigned during a complicated, one-way procedure. The mathematical algorithm used ensures that nobody (not even the system programmer) can reconstruct from the result (the 'pseudonym') the information which was used to generate the pseudonym (i.e. your unique personal data) in the first place.

The personal data transmitted to generate the pseudonym are held only for the calculation of your code name ('pseudonym') in the working memory of a large computer ('server'). The calculation of the pseudonym requires a very short time (milliseconds). Viewing personal data during this time is impossible. Thereafter 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 data base entries and every use of data is exclusively carried out under the assigned pseudonym.

Which data do I have to disclose apart from the data required to create my pseudonym in the course of the REGISTRY study and subsequent studies?

During the course of the REGISTRY study, some health and/or medical data will be recorded (see Participant Information Sheet for further details). If you are participating in any subsequent studies, your clinician will give you detailed information about the study and the data required for it accordingly. Each subsequent study requires separate participant consent.

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 terminology to you and to answer questions you may have.
2. The clinician treating you: The study site team enrolling you for REGISTRY is the only one apart from yourself who can link your pseudonym to your identifying data (i.e. name, address etc.). After generation of the pseudonym all entry of clinical information in the data base is carried out under your code name ('pseudonym'). Your study site team including your treating clinician can view all clinical data recorded under pseudonym.

3. EURO-HD staff: EURO-HD staff can view the data stored under your pseudonym in order to ensure correct documentation and high data quality to contact the study site team for clarifying questions. EURO-HD staff can only view and use pseudonymised data entered on the EURO-HD network. For the purpose of data control, staff of the EURO-HD-Network ('monitors' and 'auditors') are allowed to check with your study site team that the data entered onto the network matches with the data found in your medical records. Monitors/ auditors are bound by medical confidentiality.
4. Authorized researchers (scientist/clinicians): Scientists/clinicians who are involved in HD research can apply to the scientific review board of EHDN (a group of experienced clinicians and scientists) for authorisation to obtain access to the data base. Authorized researchers can only view coded data. To ensure the highest degree of confidentiality pseudonyms are recoded before the data bank is made available to authorized researchers. Thereby it is guaranteed that all publications reporting on the findings of authorized research exclusively use anonymised data report format (i.e. not even using the pseudonym).
5. System administrators: In order to safeguard the EURO-HD-Network central database, a small number of authorised system administrators can view pseudonymised data.
6. Other groups and individuals: No-one other than the groups and individuals described above can gain access to or receive the data stored about you.

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. This implies for all practical purposes that 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 code name ('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. A complete deletion of data is difficult, since data are likely to have become part of scientific studies and therefore need to be kept on record in compliance to laws and regulations to allow future cross checks and data verifications, even years after the research was completed. However, all links to you can be deleted and irreversibly destroyed. As a result, not even the physicians chosen by you for enrolment into REGISTRY will any longer be able to recognize data as data belonging to you. Such a complete anonymisation will be carried out in the following cases:

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

Location, date Name of the consenting clinician

Participant Model Consent Form

REGISTRY – an observational study of the European Huntington-Disease Network (EHDN)

Content, procedures, risks and aims of the research project named above as well as the right to view the data recorded was explained to me in detail by Dr ……..……..……..……..
I had the opportunity to ask questions and obtained answer which I felt were satisfactory. I had sufficient time to decide whether or not I want to participate in the project. I received a copy of the patient information and of the consent form.

Please check Yes or No for each question below, referring to the following optional study procedures:

Contact in-between study visits
I give my permission for my study site team to contact me in-between visits

- to clarify questions (e.g. concerning my answers in REGISTRY questionnaires),
- to provide me with updates on REGISTRY or
- to inform me about upcoming treatment trials for which my relative would be eligible and in which he may want to consider participation.

□ Yes □ No

Donation of blood and urine for studies to identify genetic modifiers of HD and to establish and validate biological markers for HD. Your blood sample is used as healthy control.
I give my permission for the collection of blood (20 ml or 2 tubes each containing two teaspoons) and urine (30 ml) from me and declare to donate them for scientific studies to identify genetic modifiers of HD and to establish and validate biological markers for HD. I understand that my samples are submitted to and stored at a central biorepository located in Milano (Italy) 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.

□ Yes □ No

Information and consent form regarding data protection

During scientific studies, personal data and medical findings about you are recorded. The storage, analysis and communication of data relating to the study are carried out according to legal requirements and entail the following consent before participating in the study.

3. I agree that data/medical data obtained during the course of this study can be recorded in questionnaires and on electronic data carriers and processed without providing personal identity. All pseudonymised data are stored at a server located at the University of Ulm, Germany. In addition, some selected data (pseudonym, age, sex and disease state – whether one represents a control or HD mutation carrier) will be stored at the server of the central biorepository in Milano, where the biological samples are stored.
4. I also agree that authorised persons who are bound by confidentiality (e.g. from the sponsor, or the University) 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.

Name of the Participant
……

Signature of the participant
……

Place, date……

B. Study coordination

Steering Committee

t.b.d.

Language Area Coordination (LAC)

Function	Main Contact	Location	Country	Address	Tel	Fax	Email
Central Coordination	Prof. Dr. Georg Bernhard Landwehrmeyer	Ulm	Germany	University of Ulm Neurology Oberer Eselsberg 45/1 89081 Ulm	0049 731 500 50951	0049 731 500 50966	bernhard.landwehrmeyer@medizin.uni-ulm.de
Central Coordination	Hilde Brosch	Ulm	Germany	University of Ulm Neurology Oberer Eselsberg 45/1 89081 Ulm	0049 731 500 50951	0049 731 500 50966	hilde.brosch@medizin.uni-ulm.de
Central Coordination and German LAC	Daniel Ecker	Ulm	Germany	University of Ulm Neurology Oberer Eselsberg 45/1 89081 Ulm	0049 731 500 50954	0049 731 500 50966	daniel.ecker@medizin.uni-ulm.de
German LAC	Christine Sorg	Ulm	Germany	University of Ulm Neurology Oberer Eselsberg 45/1 89081 Ulm	0049 731 500 50967	0049 731 500 50966	christine.sorg@medizin.uni-ulm.de
Netherland, Belgium and Danmark LAC	Dr. Marie-Noelle Witjes-Ané	Leiden	Netherlands	Leiden University Medical Centre (LUMC) Neurology - Section of Neuropsychology J3-R PO Box 9600 2300 RC Leiden	0031 71 5266094	0031 71 5248205	m.n.w.witjes-ane@lumc.nl
English LAC	Dr. Jenny Naji Dr. Olivia Handley	Cardiff	United Kingdom	University of Wales College of Medicine Dep of Neurology Heath Park Cardiff CF14 4XN or: Biomedical Sciences Building Museum Avenue PO Box 911 Cardiff CF10 3US	0044 2920 874112 0044 2920 743454	0044 2920 876749 0044 2920 743798	najijj@cf.ac.uk handleyo@cf.ac.uk
Italian LAC	Matilde Laurà	Milan	Italy	Istituto Neurologico Nazionale C. Besta Via Celoria 11 20133 Milan	0039 02 2394257	0039 02 2664236	mlaura@istituto-besta.it

Scandinavian	Marleen van Walsem	Oslo	Norway	Senter for Sjeldne Sykdomer og Syndromer, Rikshospitalet Forskningsveien 2B 0027 Oslo			marleenvanwalsem@yahoo.co
Spanish-Portuguese LAC	Asunción Martinez	Madrid	Spain	Fundación para Investigaciones Neurológicas Sótano. Pabellón III, Facultad de Medicina, Universidad Complutense de Madrid Avda. Complutense s/n 28040 Madrid	0034 91 3941887	0034 91 3941329	huntington@wanadoo.es asun@e-huntington.org
French LAC	Amandine Rialland	Créteil	France	Hôpital Henri Mondor Service Unité de Recherche Clinique 51 av du Maréchal de Tassigny 94010 Créteil Cedex	0033 149 813798	0033 149 813799	amdine.rialland@hmn.ap-hop-paris.fr arialland@hotmail.com

C. Hardcopy of the CRF

HD-Mutation Carrier

Demographics

Medical History

Medication Log

Comorbid Conditions

CAG Analysis

Study End and Death

UHDRS – Motor Assessment

UHDRS – Cognitive Assessment

UHDRS – Behavioral Assessment

UHDRS – Functional Assessment

UHDRS – Functional Capacity

UHDRS – Clinical Summary

Hamilton Rating Scale

Becks Depression Scale

GCI Scale

Care Giver Questionnaire

SF-36 Health Survey

Client Service Receipt Inventory

Family History

Bio Samples

Control Subjects

Demographics

Medical History

Physical Examination

Comorbid Conditions

Medication Log

Bio Samples

EURO-HD REGISTRY
DEMOGRAPHICS

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date Info Obtained: | | | . | | | . | | | | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

General

Date of 1st contact: | | | . | | | . | | | | | | | |
D D M M Y Y Y Y

Date of next visit: | | | . | | | . | | | | | | | |
D D M M Y Y Y Y

Comments:

Demographics (invariable)

Date of birth: | | | . | | | . | | | | | | | |
D D M M Y Y Y Y

Gender: |

1 = female
2 = male

Ethnicity: | |

1 = Caucasian
11 = African - Black
12 = African - North
2 = American - Black
3 = American - Latin
13 = Asian - West
14 = Asian - East
15 = mixed
6 = other
7 = unknown

Subject's statement:

Professional qualification: | |

0 = No qualification/degree
8 = CSE (8 yos)
9 = O-level (9 yos)
10 = Technical diploma
12 = University entrance diploma
14 = College
17 = Professional school degree
19 = University degree
99 = Other degree

Years of education: [years] | |

EURO-HD REGISTRY
DEMOGRAPHICS

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date Info Obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Handedness: |

1 = right
2 = left
3 = mixed

Demographics (variable)

Weight: [kg] | | | | , |

Height: [cm] | | | |

BMI: | | | | |

Occupation: |

Employment: |

0 = not employed
1 = in training
2 = employed - full time
3 = employed - part time
4 = partially unemployed
5 = unemployed
6 = maternity/parental leave
7 = military/civil service
8 = retired

Marital status: |

1 = single
2 = married
5 = partnership
3 = divorced
4 = widowed

Residence: |

1 = rural
2 = village
3 = town
4 = city

EURO-HD REGISTRY
DEMOGRAPHICS

Study Site: | | | |

Examiner: | | | | |

Subject: | | | | | | | | | | |

Date Info Obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hints:

Date of 1st contact

Enter the **date you obtained the pertinent information**. The date you enter data onto the eCRF is stored automatically - you therefore do **not** need to record it.
Example: you see a participant May 3, 2004 and you enter data (e.g. on history May 5, 2004 - **not** encouraged! Do it **right away** if at all possible!). Please enter as 'date information obtained' '03.05.2004' - this will conform to your appointment calendar and will allow verification of visits by on-site monitors.

Comments

Add a comment or notes here. The content is for your personal use only.

Gender

Refers to self-reported gender. Please comment if genetic and phenotypic/behavioural gender dissociate.

Ethnicity

The **self assigned** ethnicity - here operationalised by the area of origin - should be reported. Please ask: **'How would you describe your ethnic background?'** and **write down** the answer of your participants in the field provided.
It is understood that 'ethnicity' is not precisely defined. Ethnicity is used here to indicate shared origins, culture and traditions but not in an attempt to propose a taxonomic division of humankind by physical/genetic characteristics as implied by the term 'race'.
Examples:
- **Caucasian**: synonymous to **'white'** (e.g. British, French, German, Irish, Italian, Swedish etc.)
- **African-Black**: area of origin south of the Sahara
- **African-North**: area of origin Sahara and north of the Sahara (e.g. Algeria, Egypt, Morocco, Tunisia etc.)
- **American-Black**: people of African descent whose area of origin is within the Americas (e.g. Canada, Caribbean, Brazil, US)
- **American-Latin**:people sharing the latino culture whose area of origin is within the Americas (e.g. Mexico, South-America, US etc.)
- **Asian-West**: area of origin e.g. Bangladesh, India, Iran, Iraq, Pakistan etc.
- **Asian-East**: area of origin e.g. China, Japan, Korea etc.
-**mixed**: please indicate as precisely as possible in form of a comment (e.g. asian-white, black-white, mestizo etc.)
-**other**: please indicate as precisely as possible in form of a comment (e.g. aboriginal North-America, aboriginal Australia, semitic etc.)

Professional qualification

The **highest** qualification/degree obtained by attending school/university/any other formal training institution should be marked (irrespective of the length of time required/the ways chosen to achieve the respective professional qualification).
Note: yos = years of schooling (regular duration of schooling regardless of actual years spent in school by the respective individuum).

Years of education

Will be filled in automatically based on the entries in the field 'professional qualification'.
Note: if 'other degree' is checked, the years of education will be set to '99' - please fill in a realistic, estimated number of years on the comment page.

Handedness

Relies on the **self-report** of your participant.
Note: if a more reliable assessment is desired, please use the **Edinburgh-Inventory** (supplied as pdf). If your assessment is based on information derived from the Edinburgh Inventory (R.C. Oldfield, 1970), please indicate this fact as a **comment**.

Weight

Please **measure** (if possible) the actual weight rather than rely on the self report of the participant. Note: weight is recorded in **kg** (not pounds!).

Height

Please **measure** (if possible) the actual height rather than rely on the self report of the participant. Note: height is recorded in **cm** (e.g. 174 cm - **not** in feet or inches!).

BMI

Calculated automatically

Occupation

Please indicate as precisely as possible using the self-report of your participant (i.e. in her/his native language).

Note: refers to the type fo occupation held during **most** of her/his professional career.

Employment

Note:
- **'not employed'** refers to people who do not hold a gainful employment at the time of interview for reasons **other** than being laid off, e.g. househusband/housewife.
- **'unemployed'** refers to people who were laid off and who are seeking gainful employment.
- **'partially unemployed'** refers to people whose employers temporarily reduce working hours and consequently pay less due to shortage of orders instead of laying people off.

EURO-HD REGISTRY
DEMOGRAPHICS

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date Info Obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Residence

Self- reported categories of residence.
Rough guidelines:
-**village**: 0 - 5.000 residents
-**town**: 5.000 - 50.000 residents
-**city**: 50.000 - 10.000.0000

EURO-HD REGISTRY
MEDICAL HISTORY

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Past Medical History

Birth trauma or serious neonatal illness: | |
1 = yes
0 = no

Childhood (birth to 12 years) serious illness: | |
1 = yes
0 = no

Adolescent (13-17 years) serious illness: | |
1 = yes
0 = no

Adult (18+ years) serious illness: | |
1 = yes
0 = no

Major surgery requiring general anaesthesia: | |
1 = yes
0 = no

History of alcohol abuse: | |
1 = never abused alcohol
2 = ex-alcohol abuser
3 = currently abuses alcohol

History of drug abuse: | |
1 = never abused drugs
2 = ex-drug abuser
3 = currently abuses drugs

History of smoking tobacco: | |
1 = never smoked
2 = ex-smoker
3 = currently smokes

Is the subject naturally or surgically sterile? | |
1 = yes
0 = no

Does the subject have any allergies? | |
1 = yes
0 = no

Please list allergies: _____

_____

Does subject wear dentures? | |
1 = yes
0 = no

Study Site: ☐☐☐ Subject: ☐☐☐ ☐☐☐ ☐☐☐☐

Examiner: ☐☐☐☐ Date data obtained: ☐☐.☐☐.☐☐☐☐ (D D . M M . Y Y Y Y)

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

If yes is answered for 31a, do the dentures fit properly per the subject? ☐

1 = yes
0 = no

Psychiatric History

Depression: ☐

1 = yes
0 = no

OCD: ☐

1 = yes
0 = no

Psychosis: ☐

1 = yes
0 = no

Suicidal ideation: ☐

1 = yes
0 = no

Suicide attempts: ☐

1 = yes
0 = no

Family History

Mother affected: ☐

1 = yes
0 = no

Age at onset of symptoms in mother: [years] ☐☐

Father affected: ☐

1 = yes
0 = no

Age at onset of symptoms in father: [years] ☐☐

HD History

Symptoms first noted by subject: [mm/yyyy] ☐☐/☐☐☐☐

Symptoms first noted by family: [mm/yyyy] ☐☐/☐☐☐☐

Rater's estimate of symptom onset: [mm/yyyy] ☐☐/☐☐☐☐

HD diagnosed: [mm/yyyy] ☐☐/☐☐☐☐

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

What are these symptoms?

For the next 3 questions, please use:

1 = motor
2 = cognitive
3 = psychiatric
4 = oculomotor
5 = other
6 = mixed

Initial major symptom noted by subject: | |

Initial major symptom noted by family: | |

Rater's judgement of initial major symptom: | |

Comments: | |

1 = yes
0 = no

Enter comment: _____

_____

_____

EURO-HD REGISTRY
MEDICAL HISTORY

Study Site: | | | |

Examiner: | | | | |

Subject: | | | | | | | | | |

Date data obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hints:

Is the subject naturally or surgically sterile?

male or female

EURO-HD REGISTRY
MEDICATION LOG

Study Site: ☐☐☐

Examiner: ☐☐☐☐

Subject: ☐☐☐ ☐☐☐ ☐☐☐

Date Info Obtained: ☐☐.☐☐.☐☐☐☐ (D D . M M . Y Y Y Y)

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Medication Log

Route: 1 = p.o., 2 = p.r., 3 = s.c., 4 = i.m., 5 = i.v.

Drug name	Indication1	Indication2	Dose/Unit	Frequency	Route	Start date	Stop date
						DD.MM.YYYY	DD.MM.YYYY
						DD.MM.YYYY	DD.MM.YYYY
						DD.MM.YYYY	DD.MM.YYYY
						DD.MM.YYYY	DD.MM.YYYY
						DD.MM.YYYY	DD.MM.YYYY
						DD.MM.YYYY	DD.MM.YYYY
						DD.MM.YYYY	DD.MM.YYYY
						DD.MM.YYYY	DD.MM.YYYY
						DD.MM.YYYY	DD.MM.YYYY
						DD.MM.YYYY	DD.MM.YYYY
						DD.MM.YYYY	DD.MM.YYYY
						DD.MM.YYYY	DD.MM.YYYY
						DD.MM.YYYY	DD.MM.YYYY

EURO-HD REGISTRY
MEDICATION LOG

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date Info Obtained: | | . | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hints:

Drug name

You can either enter the **proprietory** name (= **trade name**) used in your respective country or the **generic** name. Periodically, the drug name will be coded in WHO-DD terminology by language or central coordination.

Indication1

The disorder representing the indication for use of a compound can be given in **English** or in your **native language**. Please make sure that you describe the indication **as precisely as possible**, by making use of (1) the second data field 'Indication' and (2) the 'comment' field. Periodically, your entries will be coded using the ICD10 terminology by language/central coordination.

Indication2

The second data field 'Indication' is optional. Periodically, entries will be converted to ICD10 terminology

Dose/Unit

Enter **dose** and **unit** separately, e.g. **100** and **mg** in the fields provided.

Frequency

Suggestion: Enter **102** to indicate that a drug is perscribed e.g. as 1 tablet in the morning, 0 tablets at noon and 2 tablets in the evening. Use more than 3 numbers if a compound is given more than 3 times a day. Periodically, the frequency of administration will be coded in an international convention/terminology.

Stop date

No entry in this field implies that this medication is **ongoing**. Therefore please **review** all entries **at each visit** and enter end dates if appropriate.

EURO-HD REGISTRY
COMORBID CONDITIONS

Study Site: | | | |

Examiner: | | | | |

Subject: | | | | | | | | | |

Date Info Obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Comorbid Conditions

Concomitant disorders	Start date	End date

EURO-HD REGISTRY
COMORBID CONDITIONS

Study Site: | | | |

Subject: | | | | | | | | | | |

Examiner: | | | | |

Date Info Obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hints:

Concomitant disorders

Concomitant disorders can be given in **English** or in your **native language**. Please make sure that you describe the concomitant disorder **as precisely as possible**, e.g. by making use of the comment field in addition. Periodically, your entries will be coded using the ICD10 terminology by language/central coordination

End date

No entry in this field implies that the condition is **ongoing**. Therefore please **review** all entries **at each visit** and enter end dates if appropriate.

EURO-HD REGISTRY
CAG ANALYSIS

Study Site: ☐☐☐ Subject: ☐☐☐ ☐☐☐ ☐☐☐☐

Examiner: ☐☐☐☐ Date data obtained: ☐☐.☐☐.☐☐☐☐ (D D . M M . Y Y Y Y)

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

CAG Analysis

Specimen type: ☐

1 = blood
2 = brain (postmortem)

CAG analysis results (number of CAG repeats):

Were the exact repeat lengths given in the laboratory report? ☐

1 = yes
0 = no

Allele 1 CAG repeat length (smaller allele): ☐☐☐

Allele 2 CAG repeat length (larger allele): ☐☐☐

Is the exact CAG repeat length (larger allele) known to:

The physician: ☐

1 = yes
2 = no
U = unknown

The subject: ☐

1 = yes
2 = no
U = unknown

The family: ☐

1 = yes
2 = no
U = unknown

Analyzing laboratory : _____

Comments: ☐

1 = yes
0 = no

Enter comment: _____

_____

_____

EURO-HD REGISTRY
STUDY END AND DEATH

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date of last evaluation: | | | . | | | . | | | | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

End of Study

Specify primary reason for patient's premature discontinuation from study: | |

1 = Death
2 = Event or intercurrent illness of a nature requiring withdrawal
3 = Request of primary care physician, site investigator
4 = Subject's request
5 = Failure of subject to return to follow-up visit and failure to be located by investigator
6 = Institutionalized (will not be followed further)
7 = Other, please specify:

Other reason: _____

Death Report Form:

Date of death: | | | . | | | . | | | | | | | |
D D M M Y Y Y Y

Place of death: | |

1 = home
2 = hospital
3 = nursing home
4 = hospice care
5 = unknown

Cause of death: | |

1 = pneumonia
2 = other infection
3 = cancer
4 = stroke
5 = trauma
6 = suicide
7 = other, please specify:

Other cause: _____

Was an autopsy performed? | |

0 = no
1 = yes
2 = unknown

Result of autopsy: _____

_____

_____

_____

EURO-HD REGISTRY
STUDY END AND DEATH

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date of last evaluation: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Information obtained primarily from: |

1 = spouse/family
2 = friend
3 = physician/nurse
4 = subject´s chart
5 = obituary in newspaper
6 = death certificate
7 = other

Other: _____

Comments? |

1 = yes
0 = no

Comment: _____

_____

_____

_____

EURO-HD REGISTRY
HUNTINGTON'S DISEASE RATING SCALE '99 - MOTOR ASSESSMENT

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

General

Motor score: | | | |

Motor Assessment

Ocular pursuit:

0 = complete (normal)
1 = jerky movement
2 = interrupted pursuits/full range
3 = incomplete range
4 = cannot pursue

Horizontal | | Vertical | |

Saccade initiation:

0 = normal
1 = increased latency only
2 = suppressible blinks or head movements to initiate
3 = unsupressable head movements
4 = cannot initiate saccades

Horizontal | | Vertical | |

Saccade velocity:

0 = normal
1 = mild slowing
2 = moderate slowing
3 = severely slow, full range
4 = incomplete range

Horizontal | | Vertical | |

Dysarthria:

| |

0 = normal
1 = unclear, no need to repeat
2 = must repeat to be understood
3 = mostly incomprehensible
4 = anarthria

Tongue protrusion:

| |

0 = can hold tongue fully protruded for 10 sec
1 = cannot keep fully protruded for 10 sec
2 = cannot keep fully protruded for 5 sec
3 = cannot fully protrude tongue
4 = cannot protrude tongue beyond lips

Finger taps:

0 = normal ($\geq$15/5 sec.)
1 = mild slowing, reduction in amplitude (11-14/5 sec.)
2 = moderatly impaired (7-10/5 sec.)
3 = severly impaired (3-6/5 sec.)
4 = can barly perform task (0-2/5 sec.)

Right | | Left | |

Pronate/supinate-hands:

0 = normal
1 = mild slowing and/or irregular
2 = moderate slowing and irregular
3 = severe slowing and irregular
4 = cannot perform

Right | | Left | |

EURO-HD REGISTRY
HUNTINGTON'S DISEASE RATING SCALE '99 - MOTOR ASSESSMENT

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Luria: |

0 = ≥4 in 10 sec, no cue
1 = <4 in 10 sec, no cue
2 = ≥4 in 10 sec with cues
3 = <4 in 10 sec with cues
4 = cannot perform

Rigidity-arms:

0 = absent
1 = slight or present only with activation
2 = mild to moderate
3 = severe, full range of motion
4 = severe with limited range

Right	Left

Bradykinesia-body: |

0 = normal
1 = minimally slow (?normal)
2 = mildly but clearly slow
3 = moderately slow, some hesitation
4 = markedly slow, long delays in initiation

Maximal dystonia:

0 = absent
1 = slight/intermittent
2 = mild/common or moderate/intermittent
3 = moderate/common
4 = marked/prolonged

Trunk	
RUE	
LUE	
RLE	
LLE	

Maximal chorea:

0 = absent
1 = slight/intermittent
2 = mild/common or moderate/intermittent
3 = moderate/common
4 = marked/prolonged

Face	
BOL	
Trunk	
RUE	
LUE	
RLE	
LLE	

Gait: |

0 = normal gait, narrow base
1 = wide base and/or slow
2 = wide base and walks with difficulty
3 = walks only with assistance
4 = cannot attempt

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Tandem walking: |

0 = normal for 10 steps
1 = 1 to 3 deviations from straight line
2 = >3 deviations
3 = cannot complete
4 = cannot attempt

Retropulsion pull test: |

0 = normal
1 = recovers spontaneously
2 = would fall if not caught
3 = tends to fall spontaneously
4 = cannot stand

Diagnostic Confidence

Diagnostic confidence level: |

0 = Normal (no abnormalities)
1 = non-specific motor abnormalities (less than 50 % confidence)
2 = motor abnormalities that may be signs of HD (50 - 89 % confidence)
3 = motor abnormalities that are likely signs of HD (90 - 98 % confidence)
4 = motor abnormalities that are unequivocal signs of HD $\geq$ 99 % confidence)

EURO-HD REGISTRY
HUNTINGTON'S DISEASE RATING SCALE '99 - MOTOR ASSESSMENT

Study Site: | | | | Subject: | | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hints:

Motor score

Will be calculated automatically.

Ocular pursuit

Should be assessed over a range of approximately 20° with a target passing slowly at $\leq$ 10° per second, which corresponds to about 2 seconds for moving an object from one shoulder to the other.

Saccade initiation

Should be tested over a 20° range, as for ocular pursuits. Saccade movement should be elicited by a sound (snapping fingers) or movement (wiggle fingers), but not by a verbal command to look to the right or left.

Saccade velocity

Should be tested at a larger range of approximately 30° so as to be able to detect incomplete range.

Tongue protrusion

Suggestion: Please ask your subjects to open their mouth wide while you inspect it using a torch. Then ask your subjects to protrude their tongue well beyond their front teeth while keeping their mouth wide open and to keep it out as long as it takes you (as the examiner) to count aloud from 1 to 10. Subjects should be made aware that they are not allowed to prevent their tongue from slipping back into the mouth by biting on it.

Finger taps

Subject taps thumb with index finger in rapid succession with widest amplitude possible, each hand separately.

Pronate/supinate-hands

Requires the subject to alternately hit the palmar and dorsal surface of one hand against the palm of the opposite hand. Use the palm of the opposite hand as a target instead of some other surface such as the subject´s leg or the table surface. The subject should do this task as quickly as possible over a **five-second interval**. The task is graded according to the degree of slowing and irregularity.

Luria

Fist-hand-palm sequencing - Say *'Can you do this?'* Examiner puts hand into fist on flat surface (or in lap) and sequences as follows: fist, side, flat (DO NOT REPEAT THIS OUT LOUD). Watch to make sure that subject can mimic each step. Continue to practice Luria 3-step for 1 - 2 minutes. When subject is able to join you then say *'Very good, now keep going, I am going to stop.'* Rest hand and start timing subject's sequences. A sequence is considered correct only if it is unaided by examiner model and in the correct order. Count completed sequences and score. If subject was unable to complete any sequences over a 10-second period, then continue as follows. Say *'Now lets try it again. Put your hands like this. FIST; SIDE; FLAT'*. Watch to make sure the subject can mimic each step. Using the verbal labels, begin the sequences again and ask the subject to *'Do as I do, Fist, Side, Flat'* (repeat this as you continue). Continue to perform Luria 3-step. When subject is able to join you say *'Very good, now keep going, I am going to stop'*. Rest hand and start timing subject's sequences. A sequence is considered correct if it is unaided by examiner model and in the correct order. Count completed sequences and score as above.

Rigidity-arms

Rigidity is judged on passive movement of the arms with the subject relaxed in the sitting position.

Bradykinesia-body

Observe the subject during spontaneous motion such as walking, sitting down, arising from a chair, and executing the tasks required during the examination. This rating reflects the examiner's overall impression of bradykinesia.

Maximal dystonia

Maximal dystonia is defined here as a tendency toward a posture, **posturing** along an axis. **Observe** the subject during the examination; i.e., **no particular maneuvers** are required to illicit these features. Maximal dystonia are typically observed during demanding motor tasks such as tandem gait. When rating dystonia **facial dystonia** (blepharospasm, jaw opening and closing) should be **included** in your assessment of the **truncal** region. Please indicate in a comment what subtypes of dystonia (blepharospasm, torticollis) you included in your rating of truncal dystonia. **RUE** refers to right, **LUE** to left upper extremity, **RLE** to right, **LLE** to left lower extremity.

Maximal chorea

Maximal Chorea is defined here as movement, not posture. Observe the subject during the examination; i.e., no particular maneuvers are required to illicit these features. Maximal chorea is typically observed during demanding motor tasks such as tandem gait. Chorea is rated by specific regions. **BOL** refers to buccal-oral-lingual, **RUE** to right, **LUE** to left upper extremity, **RLE** to right, **LLE** to left lower extremity. Please comment whether the chorea you observe is more distal or more proximal (e.g. distal much more than proximal).

Gait

Observe the subject walking approximately 9 meters (10 yards) as briskly as they can, then turning and returning to the starting point.

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Tandem walking

The subject is requested to walk ten steps in a straight line with the foot placed (accurately but not quickly) such that the heel touches the toe of the other foot. Deviations from a straight line are counted.

Retropulsion pull test

The subject's response to a sudden posterior displacement produced by a pull on the shoulder while the subject is standing with eyes open and feet slightly apart is assessed. The shoulder pull test must be done with a quick firm tug after warning the subject. The subject should be relaxed with feet apart and should not be learning forward. If the examiner feels pressure against his/her hands when placed on the subject's shoulders, the examiner should instruct the subject to stand up straight and not lean forward. The examiner should instruct the subject to take a step backward to avoid falling. Examiners must catch subjects who begin to fall.

Diagnostic confidence level

Is optional for the study.

EURO-HD REGISTRY
HUNTINGTON'S DISEASE RATING SCALE '99 - COGNITIVE ASSESSMENT

Study Site: | | | |

Examiner: | | | | |

Subject: | | | | | | | | | | |

Date data obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

General

Cognitive score: | | | |

Cognitive Assessment

Verbal fluency test: | | |

Symbol digit modality test: | | | |

Stroop Interference Test:

Colour naming: | | | |

Word reading: | | | |

Interference: | | | |

EURO-HD REGISTRY
HUNTINGTON'S DISEASE RATING SCALE '99 - COGNITIVE ASSESSMENT

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hints:

Cognitive score

Do not enter! Will be calculated automatically

Verbal fluency test

Subjects are asked to produce **as many words as possible** beginning with a **specified letter**. Please **download and print** a pdf-file with stimuli appropriate for your language and write down all words given by the subject in the order they are produced, even if they are incorrect or repetitions.
Time: one minute
Instructions: Say: *'I am going to say a letter of the alphabet. Then I want you to tell me as many words as you can think of that start with that letter. For instance, if I say R, you might give me rice, radio, or relish'. . . 'I do not want you to use words that start with capital letters, like Richard or Rochester. Also do not use the same word again with a different ending - if you say run, don't also say running. Any questions?'* Answer any questions the subject has about this task, then say: ***'The first letter is F** - go ahead'*. Begin timing. Should the subject give up before the end of the minute, **encourage** him/her to generate more words. If the subject is silent for more than 15 seconds, say: *'Remember, tell me words that begin with the letter . . . . . '* (and tell them the letter). Stop the subject at the end of one minute.
Continue by saying *'Now, I would like you to tell me all the words you can think of that start with the **letter 'A**"*. Administer the final **letter 'S'** the same way.
Scoring: The score is the sum of admissible responses across all three trials. Proper nouns and words not beginning with the specified letter are not counted as correct. If the subject repeats a word, count only the first occurrence of the word as correct. If multiple forms of a word are given, count only one form toward the subject's total. Vernacular or commonly accepted slang words (e.g., 'munchies') are permissible. Homonyms (e.g., 'see', 'sea') are counted separately only if the subject indicates the alternate usage. Words that are also proper nouns (e.g., 'ford') are acceptable only if the subject indicated the proper usage of the word. Since rapid transcription of words is often sloppy, scoring at a later time may be problematic due to difficulty reading one's handwriting; thus this task is best scored immediately, while the subject's responses are fresh in the mind.

Symbol digit modality test

Please **download and print** a pdf-file with stimuli and hand the sheets to the subjects. Subjects are given **90 seconds** to work on the task.
Instructions: *'Please look at the boxes at the top of the page. Each box in the upper row has a symbol in it, and each box below it has a number. Now look at the next line of boxes* (point to the first line of boxes without numbers). *Notice that the boxes on the top have symbols, but boxes beneath are empty. You are to fill in each empty box with the number that goes with each symbol according to the way they are paired at the top of the page. For example, if you look at the first symbol* (point to the first symbol in the row beneath the key), *and then look up at the key, you see that his symbol is paired with number 'one'* (show the pairing). *So you would write a 'one' in this box* (write a '1' in the first box). *This next symbol* (point to the next symbol) *is paired with five. So you would put a 'five' in this box* (write '5' in the second box). *Now what number goes in this box*(point to third box)?' When the subject appears to comprehend the task, say, *'Good, now for practice, fill in the boxes up to this double line, and then stop'* Correct immediately any errors made during the practice period, explaining the subject's error. Repeat the instructions and review the correct coding of the practice boxes as necessary until the subject understands the task. Do not administer the remainder of the test if a subject can not complete any of the practice items. Continue with the test by saying, *'When I say 'go' write in the numbers just like you have been doing as fast as you can until I say 'stop'. Work as quickly as you can moving from one line to the next without skipping any boxes. If you make a mistake, don't erase it. Just write the correct answer over the mistake. Remember to work as quickly as you can. Ready? Go!'* Start timing. At the end of 90 seconds, say*'Stop!'* Be sure that the subject does not continue working after the time limit is reached. Do not allow the subject to skip any boxes.
Scoring: The score is the number of correct responses in 90 seconds. Do not include the practice sample in the total score.

Stroop Interference Test

This test has three parts:
1) The subject **names colors** (*red, green* or *blue*).
2) The subject **reads the names of the colors** (*red, green, blue*) that appear in black print
3) The subject reads the **interference** card in which the words are printed in non-corresponding colors (e.g., *red* printed in *blue ink*), with the instructions to ignore the printed words and **report only the color of ink** in which each word is printed.

Colour naming

Time: 45 seconds
Instruction: *'Please read across the top line, naming the colors you see, either red, green, or blue'*. Occasionally a subject will incorrectly identify a color (e.g., call a blue spot 'purple'). Indicate to the subject that the three colors used in the test are red, green and blue. If the subject cannot discriminate the colors, terminate this test. Continue by pointing to the second line and say, *'Begin here, and go across the rows from left to right without skipping any. Tell me the colors as quickly as you can. Go!'* Begin timing, stop after 45 seconds.

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Scoring: Count the total number of words correctly read.

Word reading

Time: 45 seconds
Instruction: *'Please read across the top line, reading the names of the colors ('red', 'green', 'blue') that appear in black print'*. If a subject cannot read, terminate this test. Continue by pointing to the second line and say, *'Begin here, and go across the rows from left to right without skipping any. Read the names of the colors as quickly as you can. Go!'* Begin timing, stop after 45 seconds.
Scoring: Count the total number of words correctly read.

Interference

Time: 45 seconds
Instructions: *'This card has words written in colored ink, but you can see that each word is in the wrong color of ink. For example, here the word 'red' is written in blue ink* (point to the first word of the top line). *Please read across the top line, telling me the color of ink that each word is written in. Ignore the words, just tell me the color of ink you see'.* Additional review of the instructions to name ink colors and not read the words may be necessary. When it is clear that the subject understands, continue by pointing to the second line and say, *'Begin here, and go across the rows from left to right without skipping any. Remember to ignore the words, and simply tell me the colors of ink that you see. Go!'* Begin timing, stop after 45 seconds.
Scoring: Count the total number of words correctly read.

EURO-HD REGISTRY
HUNTINGTON'S DISEASE RATING SCALE '99 - BEHAVIORAL ASSESSMENT

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

General

Behavioral score: | | | |

Behavioral Assessment

Depressed mood:

Frequency: |

0 = never or almost never
1 = seldom, less than once a week
2 = sometimes, at least once a week
3 = frequently, several times a week
4 = very frequently, most of the time

Severity: |

0 = no mood disturbance
1 = questionable or equivocal
2 = mild, responds to redirection and reassurance
3 = moderately depressed, expresses distress
4 = severe, significant suffering and loss of functioning

Low self-esteem/guilt:

Frequency: |

0 = never or almost never
1 = seldom, less than once a week
2 = sometimes, at least once a week
3 = frequently, several times a week
4 = very frequently, most of the time

Severity: |

0 = no evidence
1 = questionable or equivocal
2 = mild, definitely present
3 = moderate, some distress
4 = severe

Anxiety:

Frequency: |

0 = never or almost never
1 = seldom, less than once a week
2 = sometimes, at least once a week
3 = frequently, several times a week
4 = very frequently, most of the time

Severity: |

0 = no evidence
1 = questionable or equivocal
2 = mild, responds to reassurance
3 = moderate, impacts on everyday life
4 = severe, causing a profound restriction of activities

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Suicidal thoughts:

Frequency: |

0 = not thinking about suicide or self harm
1 = seldom thinking about suicide - less than once a month
2 = sometimes thinking about suicide - at least once a month
3 = frequently thinking about suicide - at least once a week
4 = often thinks about suicide - sometimes for days and weeks on end

Severity: |

0 = no suicidal thoughts
1 = no thoughts at current time, but person talks about suicide as a potential option
2 = fleeting thoughts about it
3 = seriously considered suicide but has no plan
4 = has a plan and is actively preparing

Disruptive or aggressive behavior:

Frequency: |

0 = never or almost never
1 = seldom, less than once a month
2 = sometimes, at least once a month
3 = frequently, at least once a week
4 = very frequently, everyday

Severity: |

0 = behavior well-controlled
1 = verbal threats or intimidating behavior
2 = mild physically or verbally threatening behavior
3 = clear physical threat (moderately aggressive), bumping, shoving, verbal outburst
4 = clear physical threat (severe aggression) striking/hitting, or definite intention to cause injury

Irritable behavior:

Frequency: |

0 = never or almost never
1 = seldom, less than once a week
2 = sometimes, at least once a week
3 = frequently, several times a week
4 = very frequently, most of the time

Severity: |

0 = behavior well-controlled
1 = questionable or equivocal
2 = definite but mild
3 = moderate, others change their behavior to avoid irritating subject
4 = severe irritability

Perseverative/obsessional thinking:

Frequency: |

0 = never or almost never
1 = seldom, less than once a week
2 = sometimes, at least once a week
3 = frequently, several times a week
4 = very frequently, most of the time

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Severity: |

0 = thinking is always flexible
1 = questionable or equivocal
2 = gets stuck on certain ideas but can be easily redirected
3 = moderate - gets stuck on certain ideas, difficult to redirect
4 = severe - gets stuck on certain ideas, and does not respond to redirection

Compulsive behaviour:

Frequency: |

0 = never or almost never
1 = seldom, less than once a week
2 = sometimes, at least once a week
3 = frequently, several times a week
4 = very frequently, most of the time

Severity: |

0 = behaviour always well-controlled
1 = equivocal - has a mild impulse not sufficient to act on
2 = mild - has impulse, acts on impulse, but can stop
3 = moderate - has impulse, acts on it and sometimes cannot stop
4 = severe - has impulse, acts on it and cannot stop

Delusions:

Frequency: |

0 = no evidence
1 = seldom, less than once a month
2 = sometimes, at least once a month
3 = frequently, at least once a week
4 = very frequently, sometimes for days on end

Severity: |

0 = no evidence
1 = has delusional idea(s), not sure it is true
2 = convinced of idea(s) but allows that the idea is not true
3 = utterly convinced of the idea(s)
4 = utterly convinced of the idea(s), behavior is determined by the delusion(s)

Hallucinations:

Frequency: |

0 = no evidence of hallucinations
1 = seldom, less than once a month
2 = sometimes, at least once a month
3 = frequently, at least once a week
4 = often, sometimes for days on end

Severity: |

0 = no evidence
1 = has hallucinations, but doubts they are real
2 = convinced of the reality of the hallucinations, but allows that it is possible that they are not real
3 = utterly convinced of the hallucinations being real, but not acting on them
4 = severe - has hallucinations that are vivid, subject is utterly convinced they are real and the hallucinations severely disrupt behavior

EURO-HD REGISTRY
HUNTINGTON'S DISEASE RATING SCALE '99 - BEHAVIORAL ASSESSMENT

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Apathy:

Frequency: |

0 = never
1 = seldom apathetic, less than once a week
2 = sometimes, at least once a week
3 = frequently, several times a week
4 = very frequently, most of the time

Severity: |

0 = no evidence
1 = equivocal
2 = mild apathy - subject not initiating conversation or activity but is responsive
3 = moderate apathy - sometimes responds to efforts to get involved in conversation/activities
4 = severe apathy - generally unresponsive to attempts to involve subject in activities or conversation

Behavioral Milestones:

Does the examiner believe the subject is confused? |

1 = yes
0 = no

Does the examiner believe the subject is demented? |

1 = yes
0 = no

Does the examiner believe the subject is depressed? |

1 = yes
0 = no

Does the subject require pharmacotherapy for depression? |

1 = yes
0 = no

Does the subject require pharmacotherapy for irritability? |

1 = yes
0 = no

Information sources:

Was the behavioral assessment information obtained from: |

1 = subject only
2 = subject and family/companion

EURO-HD REGISTRY
HUNTINGTON'S DISEASE RATING SCALE '99 - BEHAVIORAL ASSESSMENT

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hints:

Behavioral score

Will be calculated automatically.

Behavioral Assessment

Instructions: Please rate the **frequency** and **severity** of the behavior for the past month. Frequency and severity should be **uniquely** assessed as independent qualifiers of positively affirmed behavioral symptoms. Frequently occurring behaviors do not indicate a high severity rating (e.g., presence of anxiety may be constant but mild in impact). Severity is indicative of the behavior's impact on the individual's ability to carry out daily activities. **["I will now ask you about experiences that most individuals have at some point in life. I will ask you to help me gauge how frequently and severely these experiences occur."]**

Depressed mood

Please ask: *In the past month have you been feeling sad (or down or blue)? Has your mood affected your daily activities? Have you found yourself doing something you would ordinarily enjoy and realized you were not having any fun?* Evidence of sad mood from behavioral observation includes sad voice or expression, tearfulness.

Low self-esteem/guilt

Please ask: *In the past month have you been feeling badly about yourself? Have you found yourself thinking or saying that you are a failure, or blaming yourself for things?* Evidence of low self-esteem/guilt includes self- blame without justification, self-deprecation including feelings of being a bad or unworthy person, feeling like a failure.

Anxiety

Please ask: *In the past month have you found yourself feeling worried about things?* Evidence if anxiety includes worrying, panic, feeling frightened or fearful for no apparent reason.

Suicidal thoughts

Please ask: *Since your last visit, have you found yourself thinking that life is not worth living or that you would be better off dead? Have you thought about hurting yourself or killing yourself? Are you planning to hurt yourself or kill yourself? Have you taken any steps toward carrying out your plan?*

Disruptive or aggressive behavior

Please ask: *Since the last visit, have you had any emotional or temper outbursts? Have you had times when you lost control of yourself? Have you hit or shoved or thrown things or expressed your temper in a physical way? Have you used threats or hostile words?* This item is used to rate loss of temper and impaired self-restraint. Threatening behavior includes physical violence or aggression, verbal outbursts, threatening, foul or abusive language.

Irritable behavior

Please ask: *In the past month, have you felt impatient? Do you behave in a demanding way? Do other say you behave in a demanding way or have a short fuse or are overly sensitive?* Note that this item is used to rate the ease with which the subject loses his/her temper rather than how extreme the behavior is once self-control is lost.

Perseverative/obsessional thinking

Please ask: *Within the past month, have you found yourself getting stuck on certain ideas? Within the past month, have you been bothered by thoughts, images or fears that keep coming back even if you try not to have them?* This item is used to rate inflexibility or perseveration of thinking. The content of the thinking need not be worries, but can be for example about making a

Compulsive behaviour

Please ask: *In the past month, have you found yourself doing certain things over and over again? Are you unable to resist doing some of these things? For example, do you wash your hands again and again, or count up to a certain number, or check that that door is locked over and over to make sure that you have done it correctly?* This item is used to rate repetitive, purposeful, and intentional behaviors.

Delusions

Please ask: *I'm going to ask you about unusual experiences that people sometimes have. Since the last visit, has it ever seemed like people are out to get you or perhaps are controlling you? Has it seemed like you have any special powers or importance, or that books, TV, and radio statements are referring to you? Are there any other unusual things you experience that I have not asked about?* Delusions are fixed false beliefs that are not culturally shared.

Hallucinations

Please ask: *Since the last visit, have you heard things that other people could not hear, such as noises or the voices of people whispering or talking? Did you ever have vision or see things that other people could not see? How about any other strange sensations in your body: skin, smell, or taste?* Hallucinations are perceptions without a physical stimulus (e.g., hearing voices when no one is in the room).

Apathy

Please ask: *Within the past month, have you found that you have lost interest in things that used to be important to you? Do you sit around a lot doing nothing? Are you just as interested as always*

in trying new things, starting new projects? Apathy is a **lack of interest or emotional involvement** in things, and can be **distinguished from anhedonia** which refers to inability to experience pleasure. Apathy is reflected **behaviorally** by **neglecting hygiene**, being **inactive**, sitting around doing nothing, **doing nothing unless told** to do it by someone else, saying little in conversation, **failing to initiate conversation**. This question should definitely be addressed to an informant if possible.

Behavioral Milestones

These items assess whether the subject has reached certain behavioral milestones.

Does the examiner believe the subject is confused?

Confusion is defined as intermittent or persistent disorganized thinking, perceptual disturbances or disorientation to time, place, or person.

Does the examiner believe the subject is demented?

Dementia is defined as progressive impairment in memory, abstract thinking or judgement that interferes with work or usual social activities and relationships.

Does the examiner believe the subject is depressed?

Depression is defined as persistent depressed mood, anhedonia, or vegetative signs sufficient to interfere with daily functioning.

EURO-HD REGISTRY
HUNTINGTON'S DISEASE RATING SCALE '99 - FUNCTIONAL ASSESSMENT

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

General

Functional Assessment Score: | |

Functional Assessment

For the next 25 questions, please use:

1 = yes
0 = no

Could subject engage in gainful employement in his/her accustomed work: |
Could subject engage in any kind of gainful employment? |
Could subject engage in any kind of volunteer or non gainful work? |
Could subject manage his/her finances (monthly) without any help? |
Could subject shop for groceries without help? |
Could subject handle money as a purchaser in a simple cash (shop) transaction? |
Could subject supervise children without help? |
Could subject operate an automobile safely and independently? |
Could subject do his/her own housework without help? |
Could subject do his/her own laundry (wash/dry) without help? |
Could subject prepare his/her own meals without help? |
Could subject use the telephone without help? |
Could subject take his/her own medications without help? |
Could subject feed himself/herself without help? |
Could subject dress himself/herself without help? |
Could subject bathe himself/herself without help? |
Could subject use public transportation to get places without help? |
Could subject walk to places in his/her neighborhood without help? |
Could subject walk without falling? |
Could subject walk without help? |
Could subject comb hair without help? |
Could subject transfer between chairs without help? |
Could subject get in and out of bed without help? |
Could subject use toilet/commode without help? |
Could subject's care still be provided at home? |

EURO-HD REGISTRY
HUNTINGTON'S DISEASE RATING SCALE '99 - FUNCTIONAL ASSESSMENT

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Information sources:

Was the functional assessment information obtained from: |

1 = subject only
2 = subject and family/companion

Independence Scale

Subject's independence in %: | | |

100 = no special care needed
95
90 = no physical care needed if difficult tasks are avoided
85
80 = pre-disease level of employment changes or ends;cannot perform household chores to pre-disease level, may need help with finances
75
70 = self-care maintained for bathing, limited household duties, e.g. cooking and use of knives, driving terminates; unable to manage finances
65
60 = needs minor assistance in dressing, toileting, bathing; food must be cut for subject
55
50 = 24-hour supervision appropriate; assistance required for bathing, eating, toileting
45
40 = chronic care facility needed; limited self feeding, liquified diet
35
30 = subject provides minimal assistance in own feeding, bathing, toileting
25
20 = no speech, must be fed
15
10 = tube fed, total bed care
5

EURO-HD REGISTRY
HUNTINGTON'S DISEASE RATING SCALE '99 - FUNCTIONAL ASSESSMENT

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hints:

Functional Assessment Score

Will be calculated automatically

Could subject engage in gainful employement in his/her accustomed work

If the subject is no longer able to work at the job he/she had for the majority of his/her life, answer 'no'. For example, if the person worked in a fast food chain as a cashier and after developing HD was forced to leave that job and worked in a less demanding job, the answer would be 'no' to gainful employment in accustomed work. If the subject is a homemaker who never worked for pay, the probe for this person might be: 'Can the subject manage the household today as well as he/she always has or must they have assistance to do so?' If assistance is now required, the answer would be 'no'.

Could subject engage in any kind of gainful employment?

Gainful employment means that the person is paid for their services. This is judged as potential capacity, not whether the person is actually working.

Could subject engage in any kind of volunteer or non gainful work?

Volunteer or non-gainful work means the person is not paid for their services.

Could subject manage his/her finances (monthly) without any help?

An informant or a subject may report that the subject has always had difficulty managing monthly finances without any help. To help to determine whether the subject could perform this activity unassisted, the probe might be:*'Compared to today, do you think he/she could have managed the monthly finances better a year ago?'* Alternatively, the probe could be *'Do you think he/she could have managed the monthly finances better before he/she had some of the symptoms/signs of HD?'* these probes which highlight change in function may help to determine the subject's capacity to perform at the present time.

Could subject shop for groceries without help?

Shopping for groceries without help means going into the store **obtaining groceries without assistance**. If the subject requires help carrying bundles, but can otherwise handle the task, the answer is 'yes'.

Could subject handle money as a purchaser in a simple cash (shop) transaction?

The person should be able to go to a shop and come back with the correct change.

Could subject supervise children without help?

Supervising children means physically as well as cognitively caring for children who could not otherwise be left alone. This does not mean infants.

Could subject operate an automobile safely and independently?

Operating an automobile safely and independently means the subject can drive without others feeling afraid to drive with the subject and showing good judgment. If the person has never learned how to drive, please file a comment indicating 'Not applicable'.

Could subject do his/her own housework without help?

Housework activities might include cooking, vacuuming, dusting, taking out the rubbish, and doing dishes. If a subject never did any housework, ask about picking up after themselves (e.g., doing light dusting or making the bed) and hanging up his/her clothes. Housework might also extend to light gardening if that was the subject's responsibility.

Could subject do his/her own laundry (wash/dry) without help?

If the subject only folds laundry and does nothing else, the answer is 'no'.

Could subject prepare his/her own meals without help?

Preparing meals can include making a sandwich, heating up soup or using the microwave, as long as the person does it himself/herself. A probe might be *'if the subject were left alone, would he/she able to prepare his/her own meals?'*

Could subject use the telephone without help?

Using a telephone without help means the ability to make outgoing calls and answer the telephone

Could subject take his/her own medications without help?

If the subject has the pills in a dispenser but he/she is able to remember to take them by himself/herself, then the answer is 'yes'. If the subject cannot physically handle medications without assistance, the answer is 'no'.

Could subject feed himself/herself without help?

If the subject cannot cut his/her own food without assistance, then the answer to ability to feed himself/herself without help is 'no'.

Could subject dress himself/herself without help?

If the subject must have clothes laid out, but he/she can dress properly (i.e., enough to be presentable), the answer is 'yes'.

Could subject bathe himself/herself without help?

If the subject requires assistance getting into the shower/tub, but then bathes himself/herself, the answer is 'yes'.

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Could subject use public transportation to get places without help?

Public transportation includes bus and train. If there is no public transportation the question should be; *'If public transportation were available, could he/she use it without assistance?'*

Could subject walk to places in his/her neighborhood without help?

Walking to places in the neighborhood without help implies not getting lost. A probe might be *'would he/she be able to find his/her way home if he/she was out on one of the streets in the neighborhood?'*

Could subject walk without falling?

Falling should occur at least once a week for a 'no' answer. A one-time fall does not indicate a 'no' answer.

Could subject walk without help?

Required use of a walker or a cane is 'help'. In other words, if the subject cannot walk without an assistive device, the answer is 'no.

Could subject's care still be provided at home?

Care at home implies only whether the person is capable of living at home, rather than in the equivalent of institutional care.

Subject's independence in %

Independence is given as percentage of normal in five percent graduations; each bullet indicates a five percent increment. If you select a bullet, the percentage will appear in the field *Independence Scale*.

EURO-HD REGISTRY
HUNTINGTON'S DISEASE RATING SCALE '99 - FUNCTIONAL CAPACITY

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

General

Functional score: | | | |

Functional Capacity

Occupation: |

0 = unable
1 = marginal work only
2 = reduced capacity for usual job
3 = normal

Finances: |

0 = unable
1 = major assistance
2 = slight assistance
3 = normal

Domestic chores: |

0 = unable
1 = impaired
2 = normal

ADL: |

0 = total care
1 = gross tasks only
2 = minimal impairment
3 = normal

Care level: |

0 = full time skilled nursing
1 = home or chronic care
2 = home

Information Sources:

Was the information obtained from: |

1 = subject only
2 = subject and family/companion

EURO-HD REGISTRY
HUNTINGTON'S DISEASE RATING SCALE '99 - FUNCTIONAL CAPACITY

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hints:

Functional score

Will be calculated automatically.

Occupation

The subject's capacity to engage satisfactorily in gainful or voluntary works is assessed regardless of whether or not the subject is actually working. **Normal** refers to gainful employment, actual or potential, with usual work expectations. **Reduced** capacity refers to full or part-time gainful employment with lower than usual work expectations (relative to the subject's training and education), but with satisfactory performance. **Marginal** refers to a capacity only for part-time employment, actual or potential with low work expectations. **Unable** refers to a subject who would be unable to carry out these financial tasks, even with considerable assistance and supervision.

Finances

Assessed by surveying the subject's involvement in personal and family finances including balancing a checkbook, paying bills, budgeting, shopping, etc. **Normal** capacity refers to satisfactory handling of these basic financial tasks. Requires **slight assistance** refers to mild difficulties which would require the assistance/supervision of a family member or financial advisor. Requires **major assistance** refers to a subject who would require extensive supervision in handling routine financial tasks. **Unable** refers to a subject who would be unable to carry out these financial tasks, even with considerable assistance and supervision.

Domestic chores

Refers to the subject's capacity to carry out routine domestic tasks such as cleaning, laundering, dishwashing, table setting, cooking, lawn care, answering mail, maintaining a calendar, etc. **Normal** capacity refers to a full capacity without assistance. **Impaired** refers to impaired capacity requiring only slight assistance or supervision. **Unable** refers to marked incapacity requiring major assistance.

ADL

Refers to the traditional areas of 'activities of daily living' (ADL) including eating, dressing and bathing. **Normal** refers to full capacity. **Minimal impairment** refers to impaired capacity requiring only slight assistance. **Gross tasks only** refers to impaired capacity requiring moderate assistance and supervision. **Total care** refers to major incapacity requiring total assistance and supervision.

Care level

Refers to the most appropriate care environment to meet the subject's capacity, whether at **home**, at **home or chronic care facility** or **full skilled nursing** care (24 hours a day supervision).

EURO-HD REGISTRY
HUNTINGTON'S DISEASE RATING SCALE '99 - CLINICAL SUMMARY

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Clinical Summary

What was the purpose of this visit? |

1 = subject in an at risk study
2 = subject in a manifest HD study
3 = presymptomatic genetic testing
4 = determine if person is symptomatic
5 = known manifest HD
6 = other

Other purpose of visit: _____

Since your last assessment of the subject, in your opinion, has the subject: |

1 = improved
2 = worsened
3 = stayed about the same
4 = not applicable (never seen before)

Since your last assessment does the subject feel: |

1 = improved
2 = worsened
3 = stayed about the same
4 = not applicable (never seen before)

Do you believe that this subject has manifest HD? |

1 = yes
0 = no

Comments: _____

_____

_____

_____

EURO-HD REGISTRY
HUNTINGTON'S DISEASE RATING SCALE '99 - CLINICAL SUMMARY

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | | | | | | | | | |
D D . M M . Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hints:

Do you believe that this subject has manifest HD?

With a confidence level $\geq$ 99% and based on UHDRS (Motor, Cognitive, Behavioral, Functional components)

EURO-HD REGISTRY
HAMILTON RATING SCALE FOR DEPRESSION

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hamilton Rating Scale

Depressed mood: |

0 = absent
1 = these feeling states indicated only on questioning
2 = these feeling states spontaneously reported verbally
3 = communicates feeling states non-verbally - i.e., through facial expression, posture, voice, and tendency to weep
4 = patient reports VIRTUALLY ONLY these feeling states in his spontaneous verbal and non-verbal communication

Feelings of guilt: |

0 = absent
1 = self reproach, feels he has let people down
2 = ideas of guilt or rumination over past errors or sinful deeds
3 = present illness is a punishment. Delusions of guilt
4 = hears accusatory or denunciatory voices and/or experiences threatening visual hallucinations

Suicide: |

0 = absent
1 = feels life is not worth living
2 = wishes he were dead or any thoughts of possible death to self
3 = suicidal ideas or gesture
4 = attempts at suicide (any serious attempt rates 4)

Insomnia early: |

0 = no difficulty falling asleep
1 = complains of occasional difficulty falling asleep - i.e., more than 1/2 hour
2 = complains of nightly difficulty falling asleep

Insomnia middle: |

0 = no difficulty
1 = patient complains of being restless and disturbed during the night
2 = waking during the night - any getting out of bed rates 2 (except for purposes of voiding)

Insomnia late: |

0 = no difficulty
1 = waking in early hours of the morning but goes back to sleep
2 = unable to fall asleep again if he gets out of bed

Work and activities: |

0 = no difficulty
1 = thoughts and feelings of incapacity, fatigue or weakness related to activities; work or hobbies
2 = loss of interest in activity; hobbies or work - either directly reported by patient, or indirect in listlessness, indecision and vacillation (feels he has to push self to work or activities)
3 = decrease in actual time spent in activities or decrease in productivity
4 = stopped working because of present illness

Retardation: Psychomotor: |

0 = normal speech and thought
1 = slight retardation at interview
2 = obvious retardation at interview
3 = interview difficult
4 = complete stupor

EURO-HD REGISTRY
HAMILTON RATING SCALE FOR DEPRESSION

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Agitation: |

0 = none
1 = fidgetiness
2 = playing with hands, hair, etc.
3 = moving about, can't sit still
4 = hand wringing, nail biting, hair-pulling, biting of lips

Anxiety: |

0 = no difficulty
1 = subjective tension and irritability
2 = worrying about minor matters
3 = apprehensive attitude apparent in face or speech
4 = fears expressed without questioning

Anxiety somatic: |

0 = absent
1 = mild
2 = moderate
3 = severe
4 = incapacitating

Somatic symptoms: |

0 = none
1 = loss of appetite but eating without encouragement from others. Food intake about normal
2 = difficulty eating without urging from others. Marked reduction of appetite and food intake

Somatic symptoms general: |

0 = none
1 = heaviness in limbs, back or head. Backaches, headache, muscle aches. Loss of energy and fatigability
2 = any clear-cut symptom rates 2

Genital symptoms: |

0 = absent
1 = mild
2 = severe

Hypochondriasis: |

0 = not present
1 = self-absorption (bodily)
2 = preoccupation with health
3 = frequent complaints, requests for help, etc.
4 = hypochondriacal delusions

Loss of weight: |

0 = no weight loss
1 = probably weight loss associated with present illness
2 = definite (according to patient) weight loss
3 = not assessed

Insight: |

0 = acknowledges being depressed and ill
1 = acknowledges illness but attributes cause to bad food, climate, overwork, virus, need for rest, etc.
2 = denies being ill at all

EURO-HD REGISTRY
HAMILTON RATING SCALE FOR DEPRESSION

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Diurnal variation:

Time of variation: |

0 = no variation
1 = worse in A.M.
2 = worse in P.M.

Severity of variation: |

0 = none
1 = mild
2 = severe

Depersonalization and derealization: |

0 = absent
1 = mild
2 = moderate
3 = severe
4 = incapacitating

Paranoid symptoms: |

0 = none
1 = suspicious
2 = ideas of reference
3 = delusions of reference and persecution

Obsessional and compulsive symptoms: |

0 = absent
1 = mild
2 = severe

EURO-HD REGISTRY
HAMILTON RATING SCALE FOR DEPRESSION

Study Site: | | | |

Subject: | | | | | | | | | | |

Examiner: | | | | |

Date data obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hints:

Depressed mood

Sadness, hopeless, helpless, worthless

Retardation: Psychomotor

Slowness of thought and speech; impaired ability to concentrate; decreased motor activity.

Anxiety

Psychological

Anxiety somatic

Physiological concomitants of anxiety, (i.e., effects of autonomic overactivity, 'butterflies', indigestion, stomach cramps, belching, diarrhea, palpitations, hyperventilation, paresthesia, sweating, flushing, tremor, headache, urinary frequency). Avoid asking about possible medication side effects (i.e., dry mouth, constipation)

Somatic symptoms

Gastrointestinal

Genital symptoms

Symptoms such as: loss of libido; impaired sexual performance; menstrual disturbances

Loss of weight

When rating by history

Time of variation

Note whether symptoms are worse in morning or evening. If NO diurnal variation, mark none.

Severity of variation

When present, mark the severity of the variation. Mark "None" if NO variation.

Depersonalization and derealization

Such as feelings of unreality; nihilistic ideas etc.

EURO-HD REGISTRY
BECKS DEPRESSION SCALE

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

General

Becks Score: | |

Beck - Depression Inventory (BDI)

A: |

0 = I do not feel sad
1 = I feel sad
2 = I am sad all the time and cannot snap out of it
3 = I am sad or unhappy that I cannot stand it

B: |

0 = I am not particularly discouraged about the future
1 = I feel discouraged about the future
2 = I feel I have nothing to look forward to
3 = I feel that the future is hopeless and that things cannot improve

C: |

0 = I do not feel like a failure
1 = I feel I have failed more than the average person
2 = As I look back on my life, all I can see is a lot of failure
3 = I feel I am a complete failure as a person; I do not feel sad

D: |

0 = I get as much satisfaction out of things as I used to
1 = I do not enjoy things the way I used to
2 = I do not get real satisfaction out of anything anymore
3 = I am dissatisfied or bored with everything

E: |

0 = I do not feel particularly guilty
1 = I feel guilty a good part of the time
2 = I feel quite guilty most of the time
3 = I feel guilty all of the time

F: |

0 = I do not feel I am being punished
1 = I feel I may be punished
2 = I expect to be punished
3 = I feel I am being punished

G: |

0 = I do not feel disappointed in myself
1 = I am disappointed in myself
2 = I am disgusted with myself
3 = I hate myself

H: |

0 = I do not feel I am worse than anybody else
1 = I am critical of myself for my weaknesses or mistakes
2 = I blame myself all the time for my faults
3 = I blame myself for everything bad that happens

EURO-HD REGISTRY
BECKS DEPRESSION SCALE

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

I: |

0 = I do not have any thoughts of killing myself
1 = I have thoughts of killing myself, but I would not carry them out
2 = I would like to kill myself
3 = I would kill myself if I had the chance

J: |

0 = I do not cry any more than usual
1 = I cry more than I used to
2 = I cry all the time now
3 = I used to be able to cry, but now I cannot cry even though I want to

K: |

0 = I am no more irritated by things than I ever am
1 = I am slightly more irritated now than usual
2 = I am quite annoyed or irritated a good deal of the time
3 = I feel irritated all the time now

L: |

0 = I have not lost interest in other people
1 = I am less interested in other people than I used to be
2 = I have lost most of my interest in other people
3 = I have lost all of my interest in other people

M: |

0 = I make decisions about as well as I ever could
1 = I put off making decisions more than I used to
2 = I have greater difficulty in making decisions than before
3 = I can not make decisions at all anymore

N: |

0 = I do not feel that I look any worse than I used to
1 = I am worried that I am looking old or unattractive
2 = I feel that there are permanent changes in my appearance that make me look unattractive
3 = I believe that I look ugly

O: |

0 = I can work about as well as before
1 = it takes an extra effort to get started at doing something
2 = I have to push myself very hard to do anything
3 = I cannot do any work at all

P: |

0 = I can sleep as well as usual
1 = I do not sleep as well as I used to
2 = I wake up 1-2 hours earlier than usual and find it hard to get back to sleep
3 = I wake up several hours earlier than I used to and cannot get back to sleep

Q: |

0 = I do not get tired more than usual
1 = I get tired more easily than I used to
2 = I get tired from doing almost anything
3 = I am too tired to do anything

EURO-HD REGISTRY
BECKS DEPRESSION SCALE

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

R: |

0 = my appetite is no worse than usual
1 = my appetite is not as good as it used to be
2 = my appetite is much worse now
3 = I have no appetite at all anymore

S: |

0 = I have not lost much weight, if any, lately
1 = I have lost more than five pounds
2 = I have lost more than ten pounds
3 = I have lost more than fifteen pounds

T: |

0 = I am no more worried about my health than usual
1 = I am worried about physical problems such as aches or pains, or upset stomach or constipation
2 = I am very worried about physical problems and it is hard to think of much else
3 = I am so worried about my physical problems that I cannot think about anything else

U: |

0 = I have not noticed any recent change in my interest in sex
1 = I am less interested in sex than I used to be
2 = I am much less interested in sex now
3 = I have lost interest in sex completely

EURO-HD REGISTRY
BECKS DEPRESSION SCALE

Study Site: | | | |

Subject: | | | | | | | | | | |

Examiner: | | | | |

Date data obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hints:

Becks Score

Will be computed automatically.

EURO-HD REGISTRY
GLOBAL CLINICAL IMPRESSION SCALE

Study Site: | | | |

Subject: | | | | | | | | | | |

Examiner: | | | | |

Date data obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Severity of Illness

Based upon my review of the information, I feel the severity of illness is: | |

0 = not assessed
1 = normal, not at all ill
2 = borderline ill
3 = mildly ill
4 = moderately ill
5 = markedly ill
6 = severely ill
7 = among the most extremely ill patients

EURO-HD REGISTRY
CARE GIVER QUESTIONAIRE

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

How well does the statement describe your feelings?

For the next 24 questions, please use:

0 = not at all
1 = only a little
2 = quite a lot
3 = a lot
4 = completely

My relative needs my help to perform many tasks: |
My relative is dependent on me: |
I have to watch my relative constantly: |
I have to help my relative constantly: |
I don't have a minute's break from my caregiving duties: |
I feel that I am missing out on life: |
I wish I could escape from this situation: |
My social life has suffered: |
I feel emotionally drained due to caring for my relative: |
I expected that things would be different at this point in my life: |
I am not getting enough sleep: |
My health has suffered: |
Caregiving has made me physically ill: |
I am physically tired: |
I don't get on with other family members as well as I used to: |
My caregiving efforts aren't appreciated by others in my family: |
I've had problems with my marriage: |
I don't do as good a job at work as I used to: |
I feel resentful of other relatives who could, but do not, help: |
I feel embarrassed by my relative's behaviour: |
I am ashamed of my relative: |
I resent my relative: |
I am uncomfortable when I have friends over: |
I feel angry about my interactions with my relative: |

EURO-HD REGISTRY
SF-36 HEALTH SURVEY

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

General

SF-36 score: | |

SF-36 Health Survey

In general, would you say your health is: |

1 = excellent
2 = very good
3 = good
4 = fair
5 = poor

Compared to one year ago, how would you rate your health in general now: |

1 = much better
2 = somewhat better
3 = about the same
4 = somewhat worse
5 = much worse

During the past 4 weeks to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours or groups: |

1 = not at all
2 = slightly
3 = moderately
4 = quite a bit
5 = extremely

During the past 4 weeks how much bodily pain have you had: |

1 = none
2 = very mild
3 = mild
4 = moderate
5 = severe
6 = very severe

During the past 4 weeks how much did pain interfere with your normal work: |

1 = not at all
2 = a little bit
3 = moderately
4 = quite a bit
5 = extremely

During the past 4 weeks how much of the time has your physical health or emotional problems interfered with your social activities like visiting friends, relatives, etc: |

1 = all of the time
2 = most of the time
3 = sometimes
4 = a little of the time
5 = none of the time

EURO-HD REGISTRY
SF-36 HEALTH SURVEY

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Does your health now limit you in these activities:

For the next 10 questions, please use:

1 = yes, a lot
2 = yes, a little
3 = not at all

Vigorous activities, such as running, lifting heavy object, participating in strenuous sports: ☐

Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf: ☐

Lifting and carrying groceries: ☐

Climbing several flights of stairs: ☐

Climbing one flight of stairs: ☐

Bending, kneeling or stooping: ☐

Walking more than a mile: ☐

Walking several blocks: ☐

Walking one block: ☐

Bathing or dressing yourself: ☐

During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of your physical health:

Cut down on the amount of time you spent on work or other activities: ☐

1 = yes
0 = no

Accomplished less than you would like: ☐

1 = yes
0 = no

Were limited in the kind of work or other activities: ☐

1 = yes
0 = no

Had difficulty performing the work or other activities: ☐

1 = yes
0 = no

During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems:

Cut down on the amount of time you spent on work or other activities: ☐

1 = yes
0 = no

EURO-HD REGISTRY
SF-36 HEALTH SURVEY

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Accomplished less than you would like: |

1 = yes
0 = no

Didn't do work or other activities as carefully as usual: |

1 = yes
0 = no

How did you feel during the past 4 weeks:

For the next 9 questions, please use:

1 = all of the time
2 = most of the time
3 = a good bit of the time
4 = some of the time
5 = a little of the time
6 = none of the time

Did you feel full of life? |

Have you been a very nervous person? |

Have you felt so down in the dumps that nothing could cheer you up? |

Have you felt calm and peaceful? |

Did you have a lot of energy? |

Have you felt downhearted and low? |

Did you feel worn out? |

Have you been a happy person? |

Did you feel tired? |

How true or false is each of the following statements for you?

For the next 4 questions, please use:

1 = definitely true
2 = mostly true
3 = don't know
4 = mostly false
5 = definitely false

I seem to get sick a little more than other people: |

I am as healthy as anybody I know: |

I expect my health to get worse: |

My health is excellent: |

EURO-HD REGISTRY
SF-36 HEALTH SURVEY

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hints:

SF-36 score

Will be calculated automatically.

During the past 4 weeks how much did pain interfere with your normal work

including both work outside the home and house-work

Had difficulty performing the work or other activities

for example, it took extra effort

During the past 4 weeks have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems

such as feeling depressed or anxious

EURO-HD REGISTRY
CLIENT SERVICE RECEIPT INVENTORY

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hospital and Residential Services

Neurology outpatient visit: |

1 = yes
0 = no

Number of attendances received in the last 6 months: | | |

Other hospital outpatient visit: |

1 = yes
0 = no

Number of attendances received in the last 6 months: | | |

Day hospital (neurology dept): |

1 = yes
0 = no

Number of attendances received in the last 6 months: | | |

Neurology inpatient ward: |

1 = yes
0 = no

Number of inpatient days received in the last 6 months: | | |

Cardiology inpatient ward: |

1 = yes
0 = no

Number of inpatient days received in the last 6 months: | | |

Urology inpatient ward: |

1 = yes
0 = no

Number of inpatient days received in the last 6 months: | | |

Intensive care unit: |

1 = yes
0 = no

Number of inpatient days received in the last 6 months: | | |

Other inpatient ward: |

1 = yes
0 = no

(specify): _____

Number of inpatient days received in the last 6 months: | | |

EURO-HD REGISTRY
CLIENT SERVICE RECEIPT INVENTORY

Study Site: ___ Subject: ___

Examiner: ___ Date data obtained: ___ (D D . M M . Y Y Y Y)

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Nursing or residential home: ___

1 = yes
0 = no

Number of residential days received in the last 6 months: ___

Primary and Community Care Services

General practitioner (GP): ___

1 = yes
0 = no

Usual location: ___

1 = care practice
2 = home

Total number of contacts: ___

Average duration: [minutes] ___

Neurologist: ___

1 = yes
0 = no

Usual location: ___

1 = care practice
2 = home

Total number of contacts: ___

Average duration: [minutes] ___

Other doctor (e.g. cardiologist): ___

1 = yes
0 = no

Usual location: ___

1 = Care practice
2 = Home

Total number of contacts: ___

Average duration: [minutes] ___

Physiotherapist: ___

1 = yes
0 = no

Usual location: ___

1 = care practice
2 = home

Total number of contacts: ___

EURO-HD REGISTRY
CLIENT SERVICE RECEIPT INVENTORY

Study Site: ☐☐☐ Subject: ☐☐☐ ☐☐☐ ☐☐☐☐

Examiner: ☐☐☐☐ Date data obtained: ☐☐.☐☐.☐☐☐☐ (D D . M M . Y Y Y Y)

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Average duration: [minutes] ☐☐☐

Social worker: ☐

1 = yes
0 = no

Usual location: ☐

1 = care practice
2 = home

Total number of contacts: ☐☐

Average duration: [minutes] ☐☐☐

Nurse: ☐

1 = yes
0 = no

Usual location: ☐

1 = care practice
2 = home

Total number of contacts: ☐☐

Average duration: [minutes] ☐☐☐

Speech therapist: ☐

1 = yes
0 = no

Usual location: ☐

1 = care practice
2 = home

Total number of contacts: ☐☐

Average duration: [minutes] ☐☐☐

Home help: ☐

1 = yes
0 = no

Usual location: ☐

1 = care practice
2 = home

Total number of contacts: ☐☐

Average duration: [minutes] ☐☐☐

Other service: ☐

1 = yes
0 = no

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

(specify): _____

Usual location: |

1 = care practice
2 = home

Total number of contacts: | |

Average duration: [minutes] | | |

Investigations / Diagnostic Tests

Magnetic Resonance Image (MRI): |

1 = yes
0 = no

Total number of investigations in the last 6 months: | |

Description (if necessary): _____

CT/CAT scan: |

1 = yes
0 = no

Total number of investigations in the last 6 months: | |

Description (if necessary): _____

Electroencephalogram (EEG): |

1 = yes
0 = no

Total number of investigations in the last 6 months: | |

Description (if necessary): _____

Blood test: |

1 = yes
0 = no

Total number of investigations in the last 6 months: | |

Description (if necessary): _____

Other investigations/tests: |

1 = yes
0 = no

Total number of investigatons in the last 6 months: | |

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Description (if necessary):

Aids or Devices

Wheelchair: |
1 = yes
0 = no

Crutches/sticks: |
1 = yes
0 = no

Stroller/zimmer frame: |
1 = yes
0 = no

Other: |
1 = yes
0 = no

(please specify):

Adaptations to the Home

Stairlift: |
1 = yes
0 = no

Shower/bath relocation: |
1 = yes
0 = no

Toilet relocation: |
1 = yes
0 = no

Redesign kitchen: |
1 = yes
0 = no

Medicalised bed: |
1 = yes
0 = no

Concrete ramp: |
1 = yes
0 = no

Other (e.g. move home): |
1 = yes
0 = no

(please specify):

EURO-HD REGISTRY
CLIENT SERVICE RECEIPT INVENTORY

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Informal Care

Personal care (e.g. bathing, dressing): |

1 = yes
0 = no

Relationship of carer to the patient: _____

Average number of hours care per week: | | | |

Help inside the home (e.g. cooking, cleaning): |

1 = yes
0 = no

Relationship of care to the patient: _____

Average number of hours care per week: | | | |

Help outside the home (e.g. shopping): |

1 = yes
0 = no

Relationship of carer to the patient: _____

Average number of hours care per week: | | | |

Other: |

1 = yes
0 = no

(specify): _____

Relationship of carer to the patient: _____

Average number of hours care per week: | | | |

What is the principal reason for extra care? |

1 = HD
2 = other illness

Have any friends and relatives stayed off work to assist with the patient's care because of HD? |

1 = yes
0 = no

For how long have they stayed off work? [total weeks] | | |

EURO-HD REGISTRY
CLIENT SERVICE RECEIPT INVENTORY

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Please estimate average income lost per week:

Currency: |

1 = EUR
2 = UK-£
3 = SFR

Amount: | | | | | | | | | | |

Journeys

Private transport (car): |

1 = yes
0 = no

Number of journeys: | | |

Number of travellers: | | |

Average distance of each return trip: [(km)] | | | | | |

Average cost of each journey per person: [EUR] | | | | |

Public transport (train, bus, etc.): |

1 = yes
0 = no

Number of journeys: | | |

Number of travellers: | | |

Average distance of each return trip: [(km)] | | | | | |

Average cost of each journey per person: [EUR] | | | | |

Hospital transport (taxi/car): |

1 = yes
0 = no

Number of journeys: | | |

Number of travellers: | | |

Average distance of each return trip: [(km)] | | | | | |

Hospital transport (ambulance): |

1 = yes
0 = no

Number of journeys: | | |

EURO-HD REGISTRY
CLIENT SERVICE RECEIPT INVENTORY

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Number of travellers: | | | |

Average distance of each return trip: [(km)] | | | | | |

Occupation

What best describes your current occupation? |

1 = employed full-time
2 = employed part-time
3 = unemployed - but available to work
4 = pensioned - through ill-health
5 = retired - through age/choice
6 = housewife/husband
7 = student

What gross wage does she/he earn?

Time unit: |

1 = /week
2 = /month
3 = /year

Currency: |

1 = EUR
2 = UK-£
3 = SFR

Amount: | | | | | | | | | | |

Have you had to stop or reduce work due to your state of ill-health? |

1 = yes
0 = no

How many days OR hours? How many days in the last 3 months? | |

How many hours per week less? | |

How long have you been unemployed/retired?

Years: | |

Months: | |

If currently not working or no longer working:

What is the reason for not/no longer working? |

1 = HD
2 = other illness
3 = not illness-related

ADMINISTRATION
FAMILY HISTORY

Study Site: | | | |

Examiner: | | | | |

Subject: | | | | | | | | | | |

Date Info Obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Spouse

Sex: |

1 = male
2 = female

Alive: |

1 = yes
2 = no
3 = unknown

If deceased:

When? year of death: | | | | | or age at death: | |

Why? _____

Participant in REGISTRY: |

1 = yes
2 = no
3 = unknown

For office use only:

Pseudonym: | | | | | | | | | | | |

ADMINISTRATION
FAMILY HISTORY

Study Site: ☐☐☐ Subject: ☐☐☐ ☐☐☐ ☐☐☐☐

Examiner: ☐☐☐☐ Date Info Obtained: ☐☐.☐☐.☐☐☐☐ (D D . M M . Y Y Y Y)

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Parents

Sex: ☐

1 = male
2 = female

Year of birth: ☐☐☐☐

Alive: ☐

1 = yes
2 = no
3 = unknown

If deceased:

When? year of death: ☐☐☐☐ or age at death: ☐☐

Why? _____

Manifest HD: ☐

1 = yes
2 = no
3 = unknown

If HD:

Age of onset of first symptoms: ☐☐

First symptoms: _____

Diagnosed by physician: ☐

1 = yes
2 = no
3 = unknown

Confirmed genetically: ☐

1 = yes
2 = no
3 = unknown

Participant in REGISTRY: ☐

1 = yes
2 = no
3 = unknown

For office use only:

Pseudonym: ☐☐☐☐☐☐☐☐☐☐☐

ADMINISTRATION
FAMILY HISTORY

Study Site: ☐☐☐ Subject: ☐☐☐ ☐☐☐ ☐☐☐☐

Examiner: ☐☐☐☐ Date Info Obtained: ☐☐.☐☐.☐☐☐☐ (D D . M M . Y Y Y Y)

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Grandparents

Parent of parent no: ☐

Sex: ☐

1 = male
2 = female

Year of birth: ☐☐☐☐

Alive: ☐

1 = yes
2 = no
3 = unknown

If deceased:

When? year of death: ☐☐☐☐ or age at death: ☐☐

Why? _____

Manifest HD: ☐

1 = yes
2 = no
3 = unknown

If HD:

Age of onset of first symptoms: ☐☐

First symptoms: _____

Diagnosed by physician: ☐

1 = yes
2 = no
3 = unknown

Confirmed genetically: ☐

1 = yes
2 = no
3 = unknown

Participant in REGISTRY: ☐

1 = yes
2 = no
3 = unknown

For office use only:

Pseudonym: ☐☐☐☐☐☐☐☐☐☐☐

ADMINISTRATION
FAMILY HISTORY

Study Site: ☐☐☐ Subject: ☐☐☐ ☐☐☐ ☐☐☐☐

Examiner: ☐☐☐☐ Date Info Obtained: ☐☐.☐☐.☐☐☐☐ (D D . M M . Y Y Y Y)

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Children

Sex: ☐

1 = male
2 = female

Year of birth: ☐☐☐☐

Alive: ☐

1 = yes
2 = no
3 = unknown

If deceased:

When? year of death: ☐☐☐☐ or age at death: ☐☐

Why? _____

HD mutation carrier: ☐

1 = yes
2 = no
3 = unknown

Manifest HD: ☐

1 = yes
2 = no
3 = unknown

If HD:

Age of onset of first symptoms: ☐☐

First symptoms: _____

Diagnosed by physician: ☐

1 = yes
2 = no
3 = unknown

Confirmed genetically: ☐

1 = yes
2 = no
3 = unknown

Participant in REGISTRY: ☐

1 = yes
2 = no
3 = unknown

For office use only:

Pseudonym: ☐☐☐☐☐☐☐☐☐☐☐

ADMINISTRATION
FAMILY HISTORY

Study Site: | | | |

Examiner: | | | | |

Subject: | | | | | | | | | | |

Date Info Obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Siblings

Child of: Father (parent no): | | Mother (parent no): | |

Sex: | |

1 = male
2 = female

Year of birth: | | | | |

Alive: | |

1 = yes
2 = no
3 = unknown

If deceased:

When? year of death: | | | | | or age at death: | |

Why? _____

HD mutation carrier: | |

1 = yes
2 = no
3 = unknown

Manifest HD: | |

1 = yes
2 = no
3 = unknown

If HD:

Age of onset of first symptoms: | |

First symptoms: _____

Diagnosed by physician: | |

1 = yes
2 = no
3 = unknown

Confirmed genetically: | |

1 = yes
2 = no
3 = unknown

Participant in REGISTRY: | |

1 = yes
2 = no
3 = unknown

For office use only:

Pseudonym: | | | | | | | | | | | |

ADMINISTRATION
FAMILY HISTORY

Study Site: | | | |

Examiner: | | | | |

Subject: | | | | | | | | | | |

Date Info Obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Nieces and Nephews

Child of sibling no: | | |

Sex: |

1 = male
2 = female

Year of birth: | | | | |

Alive: |

1 = yes
2 = no
3 = unknown

If deceased:

When? year of death: | | | | | or age at death: | |

Why? _____

HD mutation carrier: |

1 = yes
2 = no
3 = unknown

Manifest HD: |

1 = yes
2 = no
3 = unknown

If HD:

Age of onset of first symptoms: | |

First symptoms: _____

Diagnosed by physician: |

1 = yes
2 = no
3 = unknown

Confirmed genetically: |

1 = yes
2 = no
3 = unknown

Participant in REGISTRY: |

1 = yes
2 = no
3 = unknown

For office use only:

Pseudonym: | | | | | | | | | | |

ADMINISTRATION
FAMILY HISTORY

Study Site: | | | |

Examiner: | | | | |

Subject: | | | | | | | | | | |

Date Info Obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Aunts and Uncles

Sibling of parent no: | |

Sex: | |

1 = male
2 = female

Year of birth: | | | | |

Alive: | |

1 = yes
2 = no
3 = unknown

If deceased:

When? year of death: | | | | | or age at death: | |

Why? _____

HD mutation carrier: | |

1 = yes
2 = no
3 = unknown

Manifest HD: | |

1 = yes
2 = no
3 = unknown

If HD:

Age of onset of first symptoms: | |

First symptoms: _____

Diagnosed by physician: | |

1 = yes
2 = no
3 = unknown

Confirmed genetically: | |

1 = yes
2 = no
3 = unknown

Participant in REGISTRY: | |

1 = yes
2 = no
3 = unknown

For office use only:

Pseudonym: | | | | | | | | | | | |

ADMINISTRATION
FAMILY HISTORY

Study Site: | | | |

Examiner: | | | | |

Subject: | | | | | | | | | | |

Date Info Obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hints:

Spouse

Information about the **Spouse(s)** of the REGISTRY Participant (may be filled out several times, please order).

Parents

Information about the **Parents** of the REGISTRY Participant (may be filled out several times, please order).

Grandparents

Information about the **Grandparents** of the REGISTRY Participant (may be filled out several times, please order).

NOTE: Informtation is needed only from the side of the family affected by Huntington's disease.

Children

Information about the **Children** of the REGISTRY Participant (may be filled out several times, please order).

Siblings

Information about the **brothers and/or sisters** of the REGISTRY Participant (may be filled out several times, please order).

Please list all your siblings **including all half-brothers and half-sisters**, ordered by age, starting with the oldest.

Child of

Refers to parents of REGISTRY particpant only.

Nieces and Nephews

Information about the **Nieces and/or Nephews** of the REGISTRY Participant (may be filled out several times, please order).

Please list all your nieces and nephews **including the children of all half-brothers and half-sisters**. Please start by listing the children of your oldest sibling, i.e. your first entry in the table on your siblings.

Aunts and Uncles

Information about the **Aunts and/or Uncles** of the REGISTRY Participant (may be filled out several times, please order).

NOTE: Informtation is needed only from the side of the family affected by Huntington's disease.

EURO-HD REGISTRY
BIO SAMPLES

Prüfzentrum: ☐☐☐ Patient: ☐☐☐ ☐☐☐ ☐☐☐

Arzt: ☐☐☐☐ Erhebungsdatum: ☐☐.☐☐.☐☐☐☐ (D D . M M . Y Y Y Y)

Alle Felder müssen ausgefüllt werden. Verwenden Sie U für Information nicht verfügbar, N für Information nicht zutreffend.

Documents containing information on *shipping* and *courier service notification* are delievered with the bio containers **requested online** .

Note: Currently, this form is used for simulation purposes only.

Withdrawal of Specimen

Date of collection: ☐☐.☐☐.☐☐☐☐ (D D . M M . Y Y Y Y)

Time of collection: [hours/minutes] ☐☐ ☐☐

Specimen taken from fasting subject: ☐

1 = ja
0 = nein

Specimen: (1 = ja, 0 = nein)

1 tube for DNA extration/genotyping (ACD - yellow cap): ☐

1 tube for lymphoblastoid cell lines (ACD - yellow cap): ☐

1 tube for plasma (Lithium Heparine - green cap): ☐

30 ml of urine: ☐

Should CAG be determined by BioRep? ☐

1 = ja
0 = nein

Shipping

Last 3 digits of DHL shipping number: ☐☐☐

Receipt and Evaluation of Specimen

Date of receipt: ☐☐.☐☐.☐☐☐☐ (D D . M M . Y Y Y Y)

CAG smaller allele: ☐☐☐ ± ☐

CAG larger allele: ☐☐☐ ± ☐

EURO-HD REGISTRY
BIO SAMPLES

Prüfzentrum: | | | |

Arzt: | | | | |

Patient: | | | | | | | | | |

Erhebungsdatum: | | | . | | | . | | | | |
D D M M Y Y Y Y

Alle Felder müssen ausgefüllt werden. Verwenden Sie U für Information nicht verfügbar, N für Information nicht zutreffend.

Anmerkungen:

Should CAG be determined by BioRep?

Check this field only if subject has **constented** to CAG determination by BioRep and if you are taking bio samples **for the first time**.

Last 3 digits of DHL shipping number

Enter the last three digits of the DHL shipping number of the package to sent the bio samples with (for tracking reasons).

Receipt and Evaluation of Specimen

as determined by BioRep/Coriell. Do not enter at registration time!

Date of receipt

The date of receipt of the collected specimen at BioRep will be entered automtically. Do not enter at registration time.

REGISTRY CONTROL SUBJECTS
DEMOGRAPHICS

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date Info Obtained: | | . | | . | | | | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

General

Date of 1st contact: | | . | | . | | | | | | | |
D D M M Y Y Y Y

Date of next visit: | | . | | . | | | | | | | |
D D M M Y Y Y Y

Comments:

Demographics

Date of birth: | | . | | . | | | | | | | |
D D M M Y Y Y Y

Gender: |

1 = female
2 = male

Ethnicity: | |

1 = Caucasian
11 = African - Black
12 = African - North
2 = American - Black
3 = American - Latin
13 = Asian - West
14 = Asian - East
15 = mixed
6 = other
7 = unknown

Subject's statement:

Occupation:

Employment: |

0 = not employed
1 = in training
2 = employed - full time
3 = employed - part time
4 = partially unemployed
5 = unemployed
6 = maternity/parental leave
7 = military/civil service
8 = retired

REGISTRY CONTROL SUBJECTS
DEMOGRAPHICS

Study Site: | | | |

Subject: | | | | | | | | | | |

Examiner: | | | | |

Date Info Obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hints:

Date of 1st contact

Enter the **date you obtained the pertinent information**. The date you enter data onto the eCRF is stored automatically - you therefore do **not** need to record it.
Example: you see a participant May 3, 2004 and you enter data (e.g. on history May 5, 2004 - **not** encouraged! Do it **right away** if at all possible!). Please enter as 'date information obtained' '03.05.2004' - this will conform to your appointment calendar and will allow verification of visits by on-site monitors.

Comments

Add a comment or notes here. The content is for your personal use only.

Gender

Refers to self-reported gender. Please comment if genetic and phenotypic/behavioural gender dissociate.

Ethnicity

The **self assigned** ethnicity - here operationalised by the area of origin - should be reported. Please ask: **'How would you describe your ethnic background?'** and **write down** the answer of your participants in the field provided.
It is understood that 'ethnicity' is not precisely defined. Ethnicity is used here to indicate shared origins, culture and traditions but not in an attempt to propose a taxonomic division of humankind by physical/genetic characteristics as implied by the term 'race'.
Examples:

- **Caucasian**: synonymous to **'white'** (e.g. British, French, German, Irish, Italian, Swedish etc.)
- **African-Black**: area of origin south of the Sahara
- **African-North**: area of origin Sahara and north of the Sahara (e.g. Algeria, Egypt, Morocco, Tunisia etc.)
- **American-Black**: people of African descent whose area of origin is within the Americas (e.g. Canada, Caribbean, Brazil, US)
- **American-Latin**:people sharing the latino culture whose area of origin is within the Americas (e.g. Mexico, South-America, US etc.)
- **Asian-West**: area of origin e.g. Bangladesh, India, Iran, Iraq, Pakistan etc.
- **Asian-East**: area of origin e.g. China, Japan, Korea etc.
- **mixed**: please indicate as precisely as possible in form of a comment (e.g. asian-white, black-white, mestizo etc.)
- **other**: please indicate as precisely as possible in form of a comment (e.g. aboriginal North-America, aboriginal Australia, semitic etc.)

Occupation

Please indicate as precisely as possible using the self-report of your participant (i.e. in her/his native language).

Note: refers to the type fo occupation held during **most** of her/his professional career.

Employment

Note:

- **'not employed'** refers to people who do not hold a gainful employment at the time of interview for reasons **other** than being laid off, e.g. househusband/housewife.
- **'unemployed'** refers to people who were laid off and who are seeking gainful employment.
- **'partially unemployed'** refers to people whose employers temporarily reduce working hours and consequently pay less due to shortage of orders instead of laying people off.

REGISTRY CONTROL SUBJECTS
MEDICAL HISTORY

Study Site: ☐☐☐ Subject: ☐☐☐ ☐☐☐ ☐☐☐☐

Examiner: ☐☐☐☐ Date data obtained: ☐☐.☐☐.☐☐☐☐ (D D . M M . Y Y Y Y)

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Past Medical History

Birth trauma or serious neonatal illness: ☐

1 = yes
0 = no

Childhood (birth to 12 years) serious illness: ☐

1 = yes
0 = no

Adulthood (>12 years) medical conditions: ☐

1 = yes
0 = no

Medical Conditions:

Dermatological: ☐

1 = yes
0 = no

Condition: _____

Active complaint? ☐

1 = yes
0 = no

Ophthalmological: ☐

1 = yes
0 = no

Condition: _____

Active complaint? ☐

1 = yes
0 = no

Pulmonary: ☐

1 = yes
0 = no

Condition: _____

Active complaint? ☐

1 = yes
0 = no

Cardiovascular (including HTN): ☐

1 = yes
0 = no

Condition: _____

REGISTRY CONTROL SUBJECTS
MEDICAL HISTORY

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Active complaint? |

1 = yes
0 = no

Gastrointestinal: |

1 = yes
0 = no

Condition: _____

Active complaint? |

1 = yes
0 = no

Hepatic: |

1 = yes
0 = no

Condition: _____

Active complaint? |

1 = yes
0 = no

Urological: |

1 = yes
0 = no

Condition: _____

Active complaint? |

1 = yes
0 = no

Gynaecological: |

1 = yes
0 = no

Condition: _____

Active complaint? |

1 = yes
0 = no

Musculoskeletal: |

1 = yes
0 = no

Condition: _____

REGISTRY CONTROL SUBJECTS
MEDICAL HISTORY

Study Site: ☐☐☐ Subject: ☐☐☐ ☐☐☐ ☐☐☐☐

Examiner: ☐☐☐☐ Date data obtained: ☐☐.☐☐.☐☐☐☐
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Active complaint? ☐
1 = yes
0 = no

Neurological: ☐
1 = yes
0 = no

Condition: _____

Active complaint? ☐
1 = yes
0 = no

Psychiatrical: ☐
1 = yes
0 = no

Condition: _____

Active complaint? ☐
1 = yes
0 = no

Endocrine/Metabolic: ☐
1 = yes
0 = no

Condition: _____

Active complaint? ☐
1 = yes
0 = no

Other: ☐
1 = yes
0 = no

Condition: _____

Active complaint? ☐
1 = yes
0 = no

History of allergies: ☐
1 = yes
0 = no

History of alcohol abuse: ☐
1 = never abused alcohol
2 = ex-alcohol abuser
3 = currently abuses alcohol

REGISTRY CONTROL SUBJECTS
MEDICAL HISTORY

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date data obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

History of drug abuse: | |

1 = never abused drugs
2 = ex-drug abuser
3 = currently abuses drugs

History of smoking tobacco: | |

1 = never smoked
2 = ex-smoker
3 = currently smokes

REGISTRY CONTROL SUBJECTS
PHYSICAL EXAMINATION

Study Site: | | | | Subject: | | | | | | | | | | |

Examiner: | | | | | Date Info Obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Vital Signs

Weight: [kg] | | | | , |

Height: [cm] | | | |

BMI: | | | | |

Neurologic Examination

Cranial nerves abnormality? |

1 = yes
0 = no

Please specify: _____

Motor system abnormality? |

1 = yes
0 = no

Please specify: _____

Sensory system abnormality? |

1 = yes
0 = no

Please specify: _____

Tendon reflexes: BTR:

0 = -
1 = (+)
2 = + to ++
3 = +++

Right | | Left | |

Tendon Reflexes: TTR:

0 = -
1 = (+)
2 = + to ++
3 = +++

Right | | Left | |

Tendon Reflexes: PTR:

0 = -
1 = (+)
2 = + to ++
3 = +++

Right | | Left | |

Tendon Reflexes: ATR:

0 = -
1 = (+)
2 = + to ++
3 = +++

Right | | Left | |

REGISTRY CONTROL SUBJECTS
PHYSICAL EXAMINATION

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date Info Obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Pyramidal Signs: Babinski:

0 = plantar
1 = extensor

Right | | Left | |

Coordination abnormality? | |

1 = yes
0 = no

Please specify: _____

Psychiatric exploration

Depression: | |

1 = yes
0 = no

OCD: | |

1 = yes
0 = no

Psychosis: | |

1 = yes
0 = no

REGISTRY CONTROL SUBJECTS
PHYSICAL EXAMINATION

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date Info Obtained: | | . | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hints:

Weight

Please **measure** (if possible) the actual weight rather than rely on the self report of the participant. Note: weight is recorded in **kg** (not pounds!).

Height

Please **measure** (if possible) the actual height rather than rely on the self report of the participant. Note: height is recorded in **cm** (e.g. 174 cm - **not** in feet or inches!).

BMI

Calculated automatically

EURO-HD REGISTRY
COMORBID CONDITIONS

Study Site: | | | |

Examiner: | | | | |

Subject: | | | | | | | | | |

Date Info Obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Comorbid Conditions

Concomitant disorders	Start date	End date

EURO-HD REGISTRY
COMORBID CONDITIONS

Study Site: | | |

Examiner: | | | |

Subject: | | | | | | | | | |

Date Info Obtained: | | | . | | | . | | | | |

D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

EURO-HD REGISTRY
COMORBID CONDITIONS

Study Site: | | | |

Subject: | | | | | | | | | | |

Examiner: | | | | |

Date Info Obtained: | | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hints:

Concomitant disorders

Concomitant disorders can be given in **English** or in your **native language**. Please make sure that you describe the concomitant disorder **as precisely as possible**, e.g. by making use of the comment field in addition. Periodically, your entries will be coded using the ICD10 terminology by language/central coordination

End date

No entry in this field implies that the condition is **ongoing**. Therefore please **review** all entries **at each visit** and enter end dates if appropriate.

EURO-HD REGISTRY
MEDICATION LOG

Study Site: | | | |

Examiner: | | | | |

Subject: | | | | | | | | | | |

Date Info Obtained: | | | . | | | . | | | | | (D D . M M . Y Y Y Y)

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Medication Log

Route: 1 = p.o., 2 = p.r., 3 = s.c., 4 = i.m., 5 = i.v., 6 = nasal

Drug name	Indication1	Indication2	Dose/Unit		Frequency	Route	Start date (D D . M M . Y Y Y Y)	Stop date (D D . M M . Y Y Y Y)

EURO-HD REGISTRY
MEDICATION LOG

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date Info Obtained: | | . | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hints:

Drug name

You can either enter the **proprietory** name (= **trade name**) used in your respective country or the **generic** name. Periodically, the drug name will be coded in WHO-DD terminology by language or central coordination.

Indication1

The disorder representing the indication for use of a compound can be given in **English** or in your **native language**. Please make sure that you describe the indication **as precisely as possible**, by making use of (1) the second data field 'Indication' and (2) the 'comment' field. Periodically, your entries will be coded using the ICD10 terminology by language/central coordination.

Indication2

The second data field 'Indication' is optional. Periodically, entries will be converted to ICD10 terminology

Dose/Unit

Enter **dose** and **unit** separately, e.g. **100** and **mg** in the fields provided.

Frequency

Suggestion: Enter **102** to indicate that a drug is perscribed e.g. as 1 tablet in the morning, 0 tablets at noon and 2 tablets in the evening. Use more than 3 numbers if a compound is given more than 3 times a day. Periodically, the frequency of administration will be coded in an international convention/terminology.

Stop date

No entry in this field implies that this medication is **ongoing**. Therefore please **review** all entries **at each visit** and enter end dates if appropriate.

REGISTRY CONTROL SUBJECTS
BIO SAMPLES

Study Site: ☐☐☐ Subject: ☐☐☐ ☐☐☐ ☐☐☐☐

Examiner: ☐☐☐☐ Date Info Obtained: ☐☐.☐☐.☐☐☐☐ (D D . M M . Y Y Y Y)

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Documents containing information on *shipping* and *courier service notification* are delievered with the bio containers **requested online** .

Withdrawal of Specimen

Date of collection: ☐☐.☐☐.☐☐☐☐ (D D . M M . Y Y Y Y)

Time of collection: ☐☐ : ☐☐

Specimen taken from fasting subject: ☐

1 = yes
0 = no

Specimen: (1 = yes, 0 = no)

1 tube for DNA extration/genotyping (ACD - yellow cap): ☐

1 tube for lymphoblastoid cell lines (ACD - yellow cap): ☐

1 tube for plasma (Lithium Heparine - green cap): ☐

30 ml of urine: ☐

Shipping

Last 3 digits of DHL shipping number: ☐☐☐

REGISTRY CONTROL SUBJECTS
BIO SAMPLES

Study Site: | | | | Subject: | | | | | | | | | |

Examiner: | | | | | Date Info Obtained: | | . | | | . | | | | |
D D M M Y Y Y Y

All items must be completed. Use U if Information is Unavailable. Use N if Information is Not Applicable

Hints:

Last 3 digits of DHL shipping number

Enter the last three digits of the DHL shipping number of the package to sent the bio samples with (for tracking reasons).