



EUROPEAN HUNTINGTON'S DISEASE NETWORK

REGISTRY

Study Protocol

Version 3.0

Replacing Version 2.0

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

Version 3.0

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Sponsored by
European Huntington-Disease Network (EHDN)

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2 ABBREVIATIONS AND TERMS

<u>Abbreviation</u>	<u>Definition</u>
ACD	Acid citrate dextrose
CHDI	Cure Huntington's disease Initiative Foundation Inc.
Co-PI	Co-Principal Investigator
CSSR-S	Columbia Suicide Severity Rating Scale
CSRI-R	Client Service Receipt Inventory-Revised
eCRF	Electronic CRF
EHDN	European Huntington's disease Network
FHQ	Family History Questionnaire
HADS	Hospital Anxiety and Depression Scale
HD	Huntington's disease
HSG	Huntington Study Group
ICH-GCP	Good Clinical Practice according to the principles of the International Conference on Harmonisation (ICH) guidelines
IEC	Independent Ethical Committee
IRB	Institutional Review Board
PI	Principal Investigator
PBA-s	Problem Behaviours Assessment-short
QA	Quality Assurance
QC	Quality Control
SBAC	Scientific and Bioethical Advisory Committee
SF-36	Short Form-36
SI	Site Investigator
SIS	Snaith Irritability Scale
SOP	Standard Operating Procedure
TFC	Total Functional Capacity
UHDRS	Unified Huntington's Disease Rating Scale



3 SYNOPSIS

REGISTRY is a multi-centre, multi-national, prospective, observational study of Huntington's disease (HD) with a control group of volunteers. It is an open-ended study which will include as many eligible participants as willing to participate. The goal of the project is to collect longitudinal data on the phenotypical characteristics of HD gene mutation carriers regardless of whether they display clinical symptoms and signs of the disease 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 mutation carriers and individuals who are part of an HD family
- 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')
- expedite identification and recruitment of participants for clinical trials
- develop and validate sensitive and reliable outcome measures for detecting onset and change over the natural course of premanifest and manifest HD which may also be potential outcome measures for use in future clinical trials and clinical care.
- 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).

3.1 Study Schedule of Activities

Table 1a summarises the overall assessment plan for REGISTRY-HD participants. This includes individuals who are HD gene mutation carriers regardless of whether they display clinical symptoms and signs of the disease and family members who are either at risk of the disease or who have been genetically tested and are known not to carry the gene (confirmed non-mutation carriers). Table 1b summarises the overall assessment plan for REGISTRY-CONTROL participants.

Table 1a: Overall assessment plan for REGISTRY-HD participants

	Baseline visit		Annual visit
Pseudonymise	✓		
Demographics	✓		
Biosamples	✓		✓
Family History	✓		✓
Clinical/Motor	✓		✓
Behavioural	✓		✓
Cognitive	✓		✓
Quality of Life	✓		✓
Health Economics	✓		✓
Novel Assessments	✓		✓

**Table 1b: Overall assessment plan for REGISTRY-CONTROL participants**

	Baseline visit		Annual visit
Pseudonymise	✓		
Demographics	✓		
Biosamples	✓		✓
Clinical/Neurological	✓		✓
Behavioural	✓		✓
Cognitive	✓		✓
Novel Assessments	✓		✓

3.2 Participants overview

Each centre is invited to recruit as many participants as possible. Participants may include individuals with family history of HD (confirmed non-mutation carriers, mutation carriers, at risk and manifest HD), and individuals without family history of HD who may participate as REGISTRY-CONTROL participants. Companions of REGISTRY-HD participants may participate as REGISTRY-COMPANIONS.

3.3 REGISTRY Overview

3.3.1 Study title

REGISTRY

3.3.2 Type of Study

An observational, prospective, multi-national, multi-centre study of HD affected at all stages and their families including premanifest gene carriers, confirmed non-HD mutation carriers and at risk individuals, and a volunteer control group.

3.3.3 Funding

REGISTRY is funded by CHDI Foundation, Inc., New York, USA, formerly known as the High Q Foundation.

3.3.4 Sponsor

The sponsor of REGISTRY is the European HD Network (EHDN), legally represented by the University Hospital of Ulm, Germany.

3.3.5 Study Sites

Study sites in countries within and outside of Europe contribute to REGISTRY. The number of actively participating study sites is not fixed and continues to expand. For a current list of study sites, site investigators (SI's), raters and coordinators please see the EHDN website (www.euro-hd.net/html/network/locations). The selection of study sites is based on a set of criteria including interest in research in HD, prior experience in providing HD-related outpatient services, interest in participating in observational and interventional clinical studies, geographic location/catchment area, availability of appropriately trained site staff, and feasibility of the technical equipment of the study site (e.g. internet access etc.).

In order to contribute to REGISTRY in a meaningful way and to receive compensation for REGISTRY related efforts, study sites have to meet minimum qualification criteria:

- Rater training: EHDN coordinates annual rater training. Video assessments are distributed annually to study site raters who are required to submit ratings. Rating scores are reviewed by an expert panel, who award certification to the rater on the basis of scores falling within an accepted range. EHDN makes every effort to ensure that raters are certified.



Specific training material is provided for motor, cognitive and behavioural raters, Training includes video ratings, interactive training sessions, and standard operating procedures (SOPs) for test administration and scoring.

All materials for training and certification are available on the EHDN webportal (<https://www.euro-hd.net/html/registry/certification>).

- Investigator/rater credentials: EHDN Language Coordination teams obtain electronic CVs and, where appropriate, copies of medical license, records of specific training, relevant professional training.

3.3.6 Study Period

REGISTRY is an open-ended, prospective study. Participants are asked at the time of signing up for REGISTRY (= at the baseline visit) to attend as many prospective annual follow up visits as possible. In addition, participants will be asked to consider giving consent to the study site for the registration of available retrospective clinical data (e.g. UHDRS) obtained prior to enrolment in REGISTRY ('retrospective clinical data recorded from previous consultations').

3.3.7 Study Objectives

The primary goal of REGISTRY is to collect prospectively data on the phenotypical characteristics of HD mutation carriers at all stages (including the pre-motor manifest phase) 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, individuals who are part of an HD family including non-HD mutation carrying controls
- relate phenotypical characteristics with
 - genetic data ('genetic modifiers'), including a high density SNP map of all donors,
 - data derived from the study of body fluids (blood, urine – 'wet biomarker') and
 - imaging data ('dry biomarker')
- expedite identification and recruitment of appropriate participants for clinical trials
- develop and validate sensitive and reliable outcome measures for detecting onset and change over the natural course of premanifest and manifest HD which may also be potential outcome measures for use in future clinical trials and clinical care.
- 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 undergo clinical, non-invasive assessments, 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.

3.3.8 Study Population

REGISTRY-HD participants include individuals who are HD gene mutation carriers regardless of whether they display clinical symptoms and signs of the disease and family members who are either at risk of the disease or who have been genetically tested and are known not to carry the gene (confirmed non-mutation carriers). Participants may be male or female. 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 authorised representative who can provide consent.

3.3.9 Study Design

REGISTRY-HD participants are assessed at baseline and annual visits thereafter (every two years for individuals who are premanifest HD gene mutation carriers). At each visit, participants undergo clinical, motor, cognitive and behavioural assessments as well as donating blood and urine samples. REGISTRY assessments last between 30 minutes to 2.5 hours depending on the level of assessment



administered to the participant. For REGISTRY-HD participants, there are three levels of assessment varying in depth of evaluation. Table 2a defines which assessments fall into each level (minimum, core and extended). In addition, participants are invited to take part in optional components for REGISTRY (described in more detail in Section 6). REGISTRY-CONTROL participants are assessed at baseline and may be followed prospectively with annual visits. The assessments for REGISTRY-CONTROL participants fall into either a minimum or extended level of assessment (see Table 2c). REGISTRY-CONTROL participants are invited to take part in optional components for REGISTRY.

Table 2a: REGISTRY-HD Assessment Battery

		Minimum	Core	Extended	Optional*
General/Clinical	Informed consent	✓	✓	✓	
	Pseudonymisation	✓	✓	✓	
	History (medical, disease, psychiatric)	✓	✓	✓	
	Demographics (Fixed & Variable)	✓	✓	✓	
	Comorbid conditions	✓	✓	✓	
	Concomitant medication	✓	✓	✓	
	CAG report (Local Laboratory)	✓	✓	✓	
	End of study	✓	✓	✓	
	Family History				✓
Motor/Function	UHDRS '99 Motor	✓	✓	✓	
	UHDRS '99 Function (Total Functional Capacity, Function Assessment Scale, Independence Scale)	✓	✓	✓	
	UHDRS '99 Summary			✓	
	Global Clinical Impression			✓	
Behaviour	UHDRS '99 Behaviour / Problem Behaviours Assessment-Short (PBA-s)		✓	✓	
	Hospital Anxiety/ Depression Rating Scale (HADS)			✓	
	Snaith Irritability Scale (SIS)			✓	
	Columbia Suicide Severity Rating Scale			✓	
Cognitive	Brief Cognitive		✓	✓	
	Extended Cognitive			✓	
Health Economics	Client Services Receipt Inventory			✓	
Quality of Life	SF-36			✓	
Biosamples	30 ml blood, 30 ml urine				✓

*Optional components require explicit informed consent.



Table 2b: REGISTRY-COMPANION Assessment Battery

	Informed consent
Quality of Life	Caregiver questionnaire

Table 2c: REGISTRY-CONTROL Assessment Battery

		Minimum	Extended	Optional*
General/Clinical	Informed consent	✓	✓	
	Pseudonymisation	✓	✓	
	Past Medical History	✓	✓	
	Demographics (Fixed & Variable)	✓	✓	
	Comorbid conditions	✓	✓	
	Concomitant medication	✓	✓	
	End of study	✓	✓	
Motor/Function	General neurological assessment	✓	✓	
Behaviour	UHDRS '99 Behaviour / Problem Behaviours Assessment-Short (PBA-s)		✓	
Cognitive	Brief Cognitive		✓	
	Extended Cognitive		✓	
Biosamples	20 ml blood, 30 ml urine			✓

*Optional components require explicit informed consent.

REGISTRY-HD, COMPANION, and CONTROL participants are invited to participate in novel assessments (sub-studies) in addition to the assessment batteries outlined in Tables 2a-c. Further details are listed in the Summary of REGISTRY Sub-studies and a description of this component can be found in Section 6.7.

3.4 Quality Control and Quality Assurance

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

- a) the rights and well-being of human subjects are protected
- b) the reported data are accurate, complete and verifiable from source data
- c) the conduct of the trial is in compliance with the currently approved protocol/amendments and the applicable regulatory requirements (EC2001/20/EC & Directives)

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



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

EHDN has defined a REGISTRY monitoring plan and SOPs which include guidelines for the conduct of high quality epidemiological research. The monitoring plan details the data monitoring process by defining key information regarding eCRF completion, Source Data Verification, study procedures and the data flow process.

3.5 Data storage and 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 B). The identifying data are never stored electronically on the REGISTRY webportal. The investigator must store the original data and the pseudonym in the source documents (patient file) and in the investigator file.

3.6 Data flow

Data and biosamples will be stored, checked and monitored centrally by appointed data repositories and monitors.

3.7 Organisation

The Principal Investigator (PI) is Prof G. Bernhard Landwehrmeyer, Ulm, Germany who also is head of a Central Coordination team and Chief Executive Officer of the EHDN. The Co-Principle Investigator (Co-PI) is Dr Sarah Tabrizi, London, UK. The REGISTRY Steering Committee (member list is available in Appendix A and www.euro-hd.net/html/registry/steering) is responsible for finalising the study protocol. Central Coordination is responsible for implementing the protocol and liaising with sites and other agencies (data repositories, data monitors, expert advisors) to ensure that the study can be run at all sites. Where appropriate, the REGISTRY Steering Committee receives expert advice from the respective Lead Facilitator of each EHDN Working Group.

The PI of REGISTRY is responsible for:

- formulating the protocol for the study,
- organising the steering committee for the study,
- securing adequate sponsorship and support for the trial and ensuring an appropriate funding mechanism,
- subcontracting, through his or her institution, with the participating investigators and their institutions,
- subcontracting, through his or her institution, for trial coordination services,
- as appropriate, organising study subcommittees to assist in the planning and implementation of the trial.
- overseeing the implementation, and supervising the analysis and reporting for the study, and
- together with the steering committee, the accuracy of the data collected in the study.

The Co-PI of REGISTRY assists the PI in carrying out these responsibilities and assumes the responsibilities of the PI in the event that the PI is absent or incapacitated.

REGISTRY Steering Committee is responsible for:



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- selecting site investigators for the study, and for assisting the PI and Co-PI in the implementation, analysis and reporting of the study results.
- removing from active study participation any steering committee members, investigators or other study personnel who does not fulfil his/her obligations to the trial or who does not maintain the standards of EHDN with respect to confidentiality, professional conduct, rights of research subjects, conflict-of-interest, disclosure or publication policies.
- All EHDN steering committees will also ensure that trial policies governing confidentiality, human participants, clinical practice, conflict-of interest and publication are consistent with policies contained in this EHDN constitution.



4 ETHICS

4.1 Institutional Review Board or Independent Ethics Committee

The Site Investigator will provide the IRB/IEC with all appropriate material, including the protocol, the informed consent document, and other written information provided to the participants. The study will not be initiated until appropriate IRB/IEC approval of the protocol and the informed consent document and all recruiting materials are obtained in writing by Site Investigator. IRB/IEC approval will be obtained for any protocol amendments and informed consent revisions before implementing the changes.

4.2 Ethical Conduct of the Study

This study will be conducted under the principles of the World Medical Association (WMA) Declaration of Helsinki under its most recent amendment (by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000, with a Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002 and on Paragraph 30 added by the WMA General Assembly, Tokyo 2004, and including ICH-GCP guidelines). Specifically, the study will be conducted under a protocol reviewed and approved by an IRB/IEC; the study will be conducted by scientifically and medically qualified persons; the benefits of the study are in proportion to the risks; the rights and welfare of the participants will be respected; the physicians conducting the study do not find the hazards to outweigh the potential benefits; each participant will give his or her written, informed consent before any protocol-driven tests or evaluations are performed.

4.3 Participant Information and Informed Consent

A properly executed, written, informed consent, in compliance with the Declaration of Helsinki, ICH-GCP, and local regulations, will be obtained from each participant prior to entering the participant into the study. The Site Investigator will keep the original signed informed consent and place a copy of it in the participant's record file. The Site Investigator will provide copies of the signed informed consent form to each participant and caregiver (or the participant's legal representative).

The participants will be informed about the nature and importance of the study; they will receive a brief description of the foreseeable risks and discomforts and a short description of the procedures to be followed. The participants will be informed that they are free to withdraw from the study at any time without any disadvantages. Prior to the start of the study the participants will agree to the participation in the study by signing the informed consent form.

Voluntary written informed consent will be obtained from each participant at screening prior to any study related procedures. Each participant should be given both verbal and written information (in a language that is understandable to the participant) describing the meaning, aim and conduct of the study. This will take place under conditions where the participant has adequate time to consider the risks and benefits associated with his participation in the study. The participants will have the opportunity to ask all their questions. The consent will be signed and dated by the participant and the person who conducted the informed consent discussion.

It is the responsibility of the investigator to assure that informed consent is obtained from each participant in accordance with Chapter 4.8 of the ICH consolidated guideline for Good Clinical Practice from July 1996, and local regulations. The signed informed consent will be retained with the study records. Each participant will receive a copy of the signed informed consent.

4.4 Investigator Obligations

The Site Investigator (SI) agrees to conduct the clinical study in compliance with the protocol. The Site Investigator and the Sponsor should sign a REGISTRY study subcontract with the sponsor to confirm this agreement. The SI confirms that he/she has read the entire study protocol, has understood the procedures, and will comply strictly to the formulated guidelines. The SI at each site must provide on request to Central Coordination a current curriculum vitae and copies of credentials (e.g. medical license).



The SI is responsible for the adequate medical care of the participant during the study. The Investigator must follow ICH-GCP Guidelines and is responsible for the safety and the medical care of the participant.

The SI must keep a confidential list of participants, which register the pseudonym of the participants, participants' names and addresses, and their dates of birth to identify each participant at any time. The investigator also makes sure that the confidentiality of participant's data will be respected and guaranteed by all employees of the study centre.

The SI agrees that the study might be supervised by a monitor designated by the Sponsor. In this case, the SI undertakes to supply all of the necessary background information related to his/her records on request to help the monitor make a reasonable assessment of the course of the study. The SI declares him or herself ready to assist the monitor in solving all problems, which are revealed during the monitoring visit. In the event of a check, audit, or inspection, the SI will make all necessary data available to the Sponsor, monitor, auditor, or the competent authorities.

The SI has the right to request to end the study prematurely because of administrative or other circumstances. If this should occur, procedures must be established in consultation with those involved which guarantee that the interests and health-related well-being of the participation participants remain safeguarded as far as possible.

The SI or his/her medically educated representative will review the CRF for completeness and accuracy and will sign the completed CRF and any changes in the CRF. The signatures serve to attest that the information contained on the CRF is true and has not been falsified. In case of major correction the reason for it shall also be given. It is the SI's responsibility to assure completion and to review and approve all CRFs. At all times the SI has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered in the CRF.



5 ADMINISTRATIVE STRUCTURE

The study will be administered by and monitored by employees or representatives of EHDN. Clinical Research Associates will monitor the study site on a periodic basis and perform verification of source documentation for each participant.

5.1 Administrative responsibilities

A contract will be issued to regulate the obligations and rights of the investigator and the responsibilities of the REGISTRY study coordination including the sponsors; the contract will be signed between authorised 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.

The sponsor of the REGISTRY study is the EHDN, funded by CHDI Foundation, Inc.

The REGISTRY Steering Committee is responsible for overseeing the monitoring and data QC 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 personnel for this purpose. The Registry Steering Committee 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 www.euro-hd.net/html/network/project/constitution/doc). In brief, researchers interested in obtaining biosamples for further analysis have to submit brief outlines of their HD related research project to the Scientific and Bioethical Advisory Board (SBAC) of EHDN. The SBAC 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 SBAC, 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 recognise data sets as their own contribution. In parallel and prior to the release of samples confirmation is sought from the respective leading national IEC that no objections are raised against the assessment by the SBAC of EHDN that the proposed research project falls within the subject area to which participants gave their informed consent.

5.2 Study Management

Table 3 shows the roles and responsibilities designated to organisations already involved in the study.



Table 3: Study management roles and responsibilities

Role	Responsibility
Project management & planning	Central Coordination REGISTRY Steering Committee
Regulatory documents (IRB)	Central Coordination Language Coordination
Conducting investigator meetings	Central Coordination Language Coordination
Training of personnel	Central Coordination Language Coordination
Site identification and selection	Central Coordination Language Coordination REGISTRY Steering Committee
Initiation visits	Language Coordination
Monitoring visits	EHDN Monitors
Management of laboratory samples	BioRep
Quality assurance	Central Coordination BioRep



6 DETAILED STUDY DESCRIPTION

6.1 Background and rationale

HD is an autosomal-dominantly inherited, progressive neurodegenerative disorder characterised 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 (1). 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 (2). 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 (3). Systematic screening efforts to identify compounds with disease modifying properties are under way (4, 5) and some compounds have been reported to result in beneficial effects when applied in model systems of HD (6) thus providing a rationale for identifying well tolerated and clinically effective novel treatments for HD. However, currently the predictive value of these promising results obtained in model systems for HD patients 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
- relate phenotypical characteristics with
 - genetic factors ('genetic modifiers'),
 - data derived from the study of body fluids (blood, urine – 'wet biomarker') and
 - imaging data ('dry biomarker')
- expedite identification and recruitment of participants for clinical trials
- develop and validate sensitive and reliable outcome measures for detecting onset and change over the natural course of premanifest and manifest HD which may also be potential outcome measures for use in future clinical trials and clinical care.
- 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 and Bioethical Advisory Committee (SBAC) of EHDN 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 Study Group (HSG) and builds on strong collaborative relationships among basic scientists, clinical investigators and advocacy organisations for HD in the context of the EHDN, a 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 a worldwide collaborative undertaking to develop treatments that make a difference for HD. EHDN and REGISTRY are funded by the CHDI Foundation, Inc., a not-for-profit organisation 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 participants who following predictive testing are known to carry the HD mutation), and 'PHAROS' (examining phenotypes among unaffected participants 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 participants nor of participants from outside of the USA, Canada or Australia. REGISTRY will therefore provide an ongoing observational study for eligible participants who are not able to participate in PREDICT-HD or PHAROS as well as for participants 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 (7-13). The Unified Huntington's Disease Rating Scale (UHDRS) was developed by the HSG in 1993 and revised in 1999 as UHDRS 99 (14, 15). 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, which will be employed in REGISTRY, has been used in all clinical sites collaborating as HSG in North America, Europe, and Australia. The UHDRS has undergone extensive testing of reliability and internal consistency (14-16) 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 (17). The UHDRS has been used widely in HD clinical trials (18, 19).

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 (20). 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 (2, 21-24). 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 (2, 21-24). 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 (25). 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



(26). Several previous studies have reported that a gene coding for a subunit of an ionotropic glutamate receptors (GluR6; GRIK2) acts as an HD modifier (27-29). When analysed 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 (29). Findings from a recent study indicate the role of modifier gene PGC-1alpha to have a small but statistically significant amount of the variability in age of onset for the disease, which suggests that this gene has modifying effects on the pathogenic process in HD (30). Efforts are underway to systematically identify and characterise modifier genes responsible for variation in the age at onset of Huntington's disease using candidate gene approaches (e.g. htt interaction partners like UCHL1 gene and the HIP14 gene (31)) or unbiased whole genome strategies (e.g. high density SNP-maps).

Chromosomal regions harbouring additional modifier genes have been implicated by a recent genome linkage scan (the HD-MAPS study; (32-34)). Although some promising SNPs have been detected, none has so far reached genome-wide significance, suggesting that there is no single or major modifier which alone determines the variation in age of onset. 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 categorised 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.



6.2 Study objectives

To collect prospective data on the phenotypical characteristics of 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
- relate phenotypical characteristics with
 - genetic factors ('genetic modifiers'),
 - data derived from the study of body fluids (blood, urine – 'wet biomarker') and
 - imaging data ('dry biomarker')
- expedite identification and recruitment of participants for clinical trials
- develop and validate sensitive and reliable outcome measures for detecting onset and change over the natural course of premanifest and manifest HD, and which may also be potential outcome measures for use in future clinical trials and clinical care.
- 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.

6.3 Study design

All participants will be assessed at baseline and annual visits thereafter. At each visit, participants will undergo clinical, motor, cognitive and neuropsychiatric assessments as well as donating blood and urine samples. REGISTRY assessments will last between 30 minutes to 2.5 hours depending on the level of assessment administered to the participant.

In summary, REGISTRY consists of 6 components

- i. a clinical phenotypical characterisation
- ii. the collection of biological specimen
- iii. the collection of family history data
- iv. the collection of data on novel clinical assessment tools
- v. the collection of retrospective data
- vi. permission for videotaping

6.4 Clinical phenotypical characterisation

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), the PBA-s and the Columbia Suicide Severity Rating Scale (CSSR-S)¹.
- affected/HD mutation carrier/person at risk for HD themselves who self-report on their perceived quality of life (SF-36), their mood (Hospital Anxiety/Depression Rating Scale & Snaith Irritability

¹ The REGISTRY SOP for Risk Assessment for harm to self_others identifies risk indicators and protocols for personnel who consider a participant to be at risk of self harm/suicide, and/or harm to others.



Scale; HADS-SIS) and on the economic impact HD has on their lives (Client Services Receipt Inventory–Revised: CSRI-R)

- companions/care-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 UDHS '99 including a measurement of weight and height and a clinical rating scale for suicidality and harm to self or others (CSSR-S).

Specifically, the following information will be collected on REGISTRY-HD participants:

- Demographics (date of birth, gender, education, occupation, residence, marital status)
- Medical History
- Co-morbid conditions (acute and chronic, serious and non-serious)
- HD-Mutation (CAG repeat analysis, size of the alleles, laboratory performing the analysis, date of the analysis)
- Current medication
- Weight & height (+ BMI)
- UHDRS '99 motor assessment
- Cognitive assessment: a) Brief: UHDRS Cognitive (Stroop; Symbol Digit Modality Test, Letter Fluency) and Category Fluency; b) Extended: Brief version and Trail Making Test (Parts A and B), Hopkins Verbal Learning Test, and Mattis Dementia Rating Scale (optional).
- UHDRS function assessment (including Functional Assessment Scale, Independence Scale and TFC scale)
- UHDRS behavioural assessment/PBA-s

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 and mood are documented using standard tools (SF-36 for the measurement of quality of life and the HADS as a measure of depression and anxiety, and the SIS as a measure of irritability). The economic impact HD has is documented (Client Service Receipt Inventory–Revised (CSRI-R); this questionnaire is completed both by the affected/HD mutation carrier/person at risk as well as by their companions/care-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; CGQ).

At the baseline study visit, trained raters will administer the UHDRS'99 and the CSSR-S. The study participants will complete the SF-36 and the HADS-SIS. A companion (if available) will complete the CGQ and will assist in filling in the CSRI-R. In addition, at the baseline visit, participants will be asked to consider the following optional study procedures:

In REGISTRY versions 1.0 and 2.0, the protocol was confined to established instruments for participants with manifest disease (showing features of the disease currently defined as diagnostic). The UHDRS and the other assessments evaluated in REGISTRY 3.0 are geared towards capturing the phenotype displayed by this population but do not adequately capture the more subtle but clearly quantifiable symptoms and signs of individuals approaching the onset of motor signs. Both PREDICT-HD (35) and TRACK-HD (36) have established unequivocally that there are abnormalities that have a functional impact in all three domains (cognitive, behavioural, and motor) if assessed with sensitive instruments. In addition, these clinical phenotypical alterations are correlated with clearly measurable changes in regional brain volumes as assessed by MR imaging (35, 37, 38).

Likewise, the UHDRS does not allow a meaningful assessment for the advanced stages of HD for a number of reasons. For example, the standard UHDRS cognitive assessment consisting of timed psychomotor tasks, cannot be administered to people in more advanced stages of HD due to their motor impairment and dysarthria. Therefore, an important component of the cognitive phenotype is very often not assessed in the advanced stage HD participants. Likewise, communication impairments preclude an interview-based behavioural assessment. Lastly, the motor phenotype for all items of the



motor scale, requiring active participation by the participant is not informative in more advanced stages. Other aspects like impaired mobility and control over bodily functions that contribute greatly to the caregiver burden and the medical needs of advanced stages of HD are not captured in the standard UHDRS assessment. Therefore REGISTRY version 3.0 contains a sub-study assessment of advanced stage HD based on the pioneering scale development led by Prof. Anne-Catherine Bachoud Levi and Prof. Raymund Roos (see supplementary document Summary of REGISTRY Sub-studies).

Finally, expansion mutation carriers with very large CAG expansions (>55 repeats) present clinically early (Juvenile HD) and with a distinct phenotype that is not captured completely by the items of the current version of UHDRS, which was originally developed to assess the most prevalent phenotype which is the adult onset of the disease. Therefore, a modified and expanded UHDRS scale is proposed by the EHDN Juvenile HD WG to be tested on a broader scale in the context of REGISTRY 3.0 (see supplementary document Summary of REGISTRY Sub-studies).

Assessment scales and questionnaires to capture specific clinical phenotypes of HD are under development and will be validated as part of REGISTRY sub-studies. Once validated as sensitive and reliable measures that can be administered cross-culturally, the assessment tools will become available to the HD community and will be accepted as part of the standard REGISTRY assessment for the relevant population groups.

6.5 Collection of biological specimen

Donation of biological specimens – 30ml of blood and 30 ml of urine – at the baseline visit and at each annual visit. 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.

First REGISTRY visit:

All sites:

Every site is encouraged to take 20ml of blood to obtain the following:

- 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. Samples for DNA and lymphoblastoid cell lines will be taken only once at the first visit, unless directed by BioRep that generation of lymphoblastoid cells lines failed, in which case a further sample will be collected.
- Urine (30 ml) for studies to establish and validate markers tracking the progressive course of HD (e.g. metabolomics)

Selected sites

- Participants will be asked to donate blood for plasma collection. The amount required is 9.5ml. Precise time of day of collection will always be documented, and whether the participant is fasting (no food/drink for 8 hours) or non-fasting. From 9.5 ml whole blood, ~6 ml plasma is collected.

Subsequent REGISTRY visits:

All sites:



Every site is encouraged to take 10 ml of blood to obtain the following:

- All participants will be asked to donate 10 ml of blood for the preparation of lymphocytes.
- Urine (30 ml) for studies to establish and validate markers tracking the progressive course of HD (e.g. metabolomics)

Selected sites:

- Participants will be invited to donate blood in for plasma collection. The amount required is 9.5ml. Precise time of day of collection will always be documented, and whether the participant is fasting (no food/drink for 8 hours) or non-fasting. From 9.5 ml whole blood, ~6 ml plasma is collected.

To extract good quality plasma, blood samples will be processed on-site without delay according to a validated SOP (REGISTRY SOP for Plasma Collection). Plasma samples will be divided it into 500µL aliquots for freezing at -80C. All plasma collection kits will be provided by BioRep on a per-patient basis. Plasma samples are stored locally at -80C until shipment on dry ice to BioRep at regular time points.

Note: the result of the genotyping by BioRep will be made available to the study site which sent the specimen to the BioRep. 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 periodically receive a CAG data update from Central Coordination. This update tabulates results from the CAG page of the REGISTRY CRF against the results reported by BioRep. 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. Such discrepancies and the recommendation for a third independent genetic test are communicated on a case-by-case basis to the Site PI and relevant site staff. Central Coordination highlights any potential implications for the participant's HD status. The procedures for handling discrepancies are described in an SOP (SOP Guidelines for BioRep CAG results communication to sites).

6.6 Completion of a family history questionnaire (FHQ)

All participants will be invited to complete a FHQ, in particular individuals who do not have a known family history of the disease. This is an optional component of REGISTRY. 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 (spouses). 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. An interview or 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
- local availability of DNA samples

From these data a family tree will be generated using appropriate software (SOP for creation of Family History Tree). 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 they 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 biosamples 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 choose 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.

Authorised 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.

6.7 Sub-studies

Clinical experience, the activities of EHDN working groups and REGISTRY data-mining projects have prompted the use of established and not yet established assessments to better inform us about specific and/or rare clinical phenotypes not presently captured in the existing standardised assessments REGISTRY version 3.0. The benefits of validating assessment tools can be summarised as follows: To explore whether additional assessments are useful (clinically and for research purposes); Validation of the assessment tools is an iterative process and implies that a first best guess instrument is applied, providing us with a starting point to explore the clinical metrics of these assessments as well as inter-rater reliability. Systematic review of each scale will assist in the development of an improved, revised assessment tool. The first phase will follow a cross-sectional study design, and the second phase will extend to a longitudinal study to look at the rate of changes in the various assessments.

Participants have the option to participate in the REGISTRY sub-studies. These sub-studies permit the collection of data on assessment tools to be carried out in an expedient, time-efficient manner. Each REGISTRY sub-study follows an iterative process in order to fulfil task validation. That is, statistical analyses will be carried out at specific time-points in order to review task sensitivity and reliability (intra- and inter-rater reliability), with the aim of refining (and wherever possible shortening) the assessment tool ahead of broader use in the HD clinical and research setting. Once sufficient data have been obtained to achieve pre-specified power, statistical analyses will determine the validity of the assessment tool. Each assessment will undergo a formal review by the REGISTRY Steering Committee (with the expert advice from respective Lead Facilitator of each Working Group).

The REGISTRY sub-studies component is flexible (see Summary of REGISTRY's Sub-Studies, supplementary document). A list of the assessments is provided as a supplement to this document. It outlines the nature of each task and the estimated time to complete the assessments. The ongoing review and scale development will in many cases result in modifications to assessments. Such changes will be regarded as changes to the internal procedures with no added burden on participant time. Validated assessment tools will be implemented into REGISTRY standard assessment. Therefore the assessment protocol is likely to change as new tests become available.

The aim will be to identify and validate additional clinical outcome measures either associated with a specific state of the disease or describing specific domains of the disease, e.g. cognition, behaviour and function. Once fully validated, these additional assessments may serve as sensitive and reliable outcome measures for clinical trials.

In an attempt to take full advantage of the extent of the Network, participation in the REGISTRY sub-studies is widely available. This will promote the timely collection of data and increase the enrolment of adequate numbers for studies of rarer phenotypes, e.g. specific symptoms, such as irritability, apathy, or rare phenotypes, e.g. juvenile-onset HD. Participants are invited to participate in REGISTRY 'sub-studies' as part of a collaborative effort to validate novel assessment tools for use in clinical and research domains. The procedures and assessments are non-invasive and have minimal burden on the participant. A participant may choose to opt in or opt out of the optional component. The REGISTRY study assessment time should not exceed 2.5 hours. The conduct of each sub-study will follow administrative guidelines set out in SOPs. Each sub-study has a task force to coordinate the training, data collection and statistical analysis, and is charged with the responsibility to distribute the findings from the sub-study in a peer-reviewed publication.

6.8 Retrospective data collection

Participants will be specifically asked for their permission to enter clinical data prior to the date of enrolment to REGISTRY, and they will be at liberty to contribute to the prospective study only. Multiple study sites have systematically collected assessments of HD patients using standard tools (e.g. UHDRS) that were generated either in the course of their normal clinical practice or during the course of conducting HD-related research projects. In order to allow the research community to have access to



these systematically collected clinical data, recorded prior to participation in REGISTRY, study sites have the option to request permission from REGISTRY-HD participants to enter these data. The collection of retrospective data will significantly enrich the clinical data repository available on this HD cohort. The combination of retrospective and prospective clinical data will provide a unique and invaluable resource that can be used to understand more about clinically significant changes over the natural course of HD. Consent to providing these data is no additional burden on the participant. A participant may choose to opt in or opt out of this optional component.

6.9 REGISTRY assessments

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

- a) Clinical phenotypical characterisation will be assessed and documented based on information obtained from:
 - Trained raters who record their clinical impression using rating scales (i.e. UHDRS'99, the PBA-s and cognitive tests; CSSR-S).
 - Participants themselves who report on their subjective experience (i.e. HADS-SIS, SF-36 and a health economics scale (CSRI-R))
 - Partners/Companions who report on the level of function and neuropsychiatric aspects of the participant, and quality of life.
- b) Donation of biological specimens – 30 ml of blood and 30 ml of urine (REGISTRY-HD participant); 20 ml of blood and 30 ml of urine (REGISTRY-CONTROL participant).
- c) Completion of a family history questionnaire (FHQ).

All participants will be invited to complete a FHQ, in particular individuals who do not have a known family history of the disease. This is an optional component of REGISTRY. 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 three generations will be assembled as well as data on the spouse (spouses). 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 ensure an appropriate number of linked biosamples and linked clinical data sets, participants are asked (provided that they feel comfortable to do so) to forward an invitation to their relatives to consider taking part in REGISTRY.

- d) 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.
- e) Participants will be asked to give their consent for registration of their retrospective data gathered during consultations prior to their participation for REGISTRY, providing that these data were assessed with the same tools.
- f) Participants will be asked to give their consent to take part in the Novel Assessment Protocol. This will permit the collection of data on novel assessments tools.
- g) Participants will be asked to consider giving their consent to videotaping. The videotapes will be visible for a restricted number of EHDN members (e.g. experienced physicians, for consultation purposes, physicians in training) for quality control, research and training purposes only. The recordings will be transmitted via secure internet connection and will be stored on the REGISTRY server in a pseudonymised form.



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

- a) a clinical phenotypical characterisation identical to the one at baseline 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.

REGISTRY-HD participants who consented to donate biological specimens and to volunteer the family history will be requested to:

- b) donate a next sample of biological specimens (30 ml of blood and 30 ml of urine)
- c) 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.

6.10 Observation schedules

Investigators should evaluate REGISTRY-HD 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 visit, the following will take place:

A clinical phenotypical characterisation 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.

REGISTRY-HD 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
- donate a sample of biological specimens– 30 ml of blood and 30 ml of urine – to obtain the following materials:
 - One 10 ml tube of blood for the cryopreservation of lymphocytes (collected annually)
 - One 10 ml tube of blood to confirm the size of the CAG expansion mutation within the HD gene for research purposes only and to create lymphoblastoid cell lines.
 - One 9.5 ml tube of whole blood (EDTA) for plasma collection (collected annually at selected sites)
 - 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 REGISTRY Steering Committee, 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. An SOP for Plasma Collection is in place to ensure consistency in procedures across sites collection plasma samples.

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 maximise participant retention in the study. REGISTRY HD 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.

6.11 Description of the study population

6.11.1 Participant selection criteria

REGISTRY-HD participants include 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), are non-HD mutation carrier relatives. Spouses of participants may take part as REGISTRY-CONTROLS.

Inclusion criteria

The following individuals may be eligible to participate

- A. Individuals, confirmed HD mutation carrier
- B. Manifest HD, without CAG testing
- C. HD family member at-risk, without CAG testing
- D. HD family member, non-HD mutation carrier
- E. REGISTRY-CONTROL participants: companion/individual without HD history
- F. REGISTRY-COMPANION (any of the above).

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 authorised legal representative who can provide consent.

Note on vulnerable participants and participants 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 participant 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 authorised legal representative.

Exclusion criteria

- Participants 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. (EHDN provides a Registry-like tool to record findings in patients affected with choreatic movement disorders other than HD under the label "Neuroacanthocytosis"; www.euro-hd.net/html/na/registry).



6.12 Method of Identification and Recruitment of study participants

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

6.13 Participant informed consent

The research staff at the study sites will seek consent from any eligible participant 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 B) 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 participant 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 participant'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 cognisant and be able to understand the procedures, risks, and benefits involved with the study. At the time of the participant's visit, an explanation of the study and a copy of the consent will be provided to both the participant and the authorised representative. Opportunity to read the consent will be given and questions answered by the research staff. The participant/authorised 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 authorised representative will be officially providing consent for the participant to participate, the participant 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 participant 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 participant who begins participation in this study as a minor (under the age of 18) will be asked to re-consent for this study after turning 18 years of age.

For the UK, the Mental Capacity Act requires specific procedures which are described below.

If a potential participant with mental incapacity is approached for enrolment, the research staff will identify an appropriate consultee who can advise on the presumed wishes and feelings of the participant.



Identifying a consultee

The following steps will be taken in order to identify a suitable consultee:

- If an unpaid carer (e.g. spouse or family member) can be identified and they are willing to be involved, they will have the research explained to them and will be asked for their advice on involving the person in the research. The consultee must be someone who knows the potential participant well and who will be able to give an opinion about the person's presumed wishes and feelings.
- If the carer attending the research appointment is a health care professional, then attempts will be made to find a friend or family member (or someone with Lasting Power of Attorney (LPA) for the person) who knows the person well and they will be asked for their advice.
- If there is no unpaid carer, friend or family member and no-one with LPA then a consultee who is not involved with the project will be nominated. An independent consultee could either be identified by the clinical research team or the Huntington's disease Association Regional Care Advisor (RCA). In some instances, the RCA may also be willing to provide advice on behalf of the participant and is an independent person who could either act as consultee or assist in identifying someone familiar with HD to act in this role.

Invitation to participate in research

The following steps will be taken to discuss the research with the consultee and the potential participant:

- An explanation of the study and a copy of the patient information sheet, consultee information sheet and patient consent form will be provided to both the participant and the consultee.
- Carers or nominated third parties must be consulted and agree that the person would want to join the research project. In particular, the consultee should advise about:
 - whether the person who lacks capacity should take part in the project, and what they think the person's feelings and wishes would be, if they had capacity to decide whether to take part.
- If the person shows any signs of resistance or indicates in any way that he or she does not wish to take part, the person must be withdrawn from the project immediately.
- Sometimes the consultee will say that the person would probably not take part in the project or that they would ask to be withdrawn. In this situation, the researcher must not include the person in the project, or they should withdraw them from it
- Even when a consultee agrees that a person can take part in research, the researcher must pay extra attention to monitoring the person's wishes and feelings.

If participants lose mental capacity during the course of this study the above steps will also be taken to identify a suitable consultee who can advise on the presumed wishes of the participant.

6.14 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 participant/parent/guardian and, if applicable, their authorised representative.

6.15 Study Procedures - Descriptions

6.15.1 Clinical Characteristics

The clinical characteristics questionnaire will capture essential and more detailed information of when signs and symptoms first appear. The examiner is instructed to provide a best estimate onset age for a range of clinical features. Data obtained from this questionnaire will permit future studies to evaluate the extent to which other genetic or environmental modifiers influence the age of onset of symptoms other than the movement disorder in HD.



6.15.2 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 consists of four parts: cognition, motor function, behaviour, and functional capacity. Modified versions of these scales and other scales may be used where these may be appropriate for measuring the progression of HD in patients of other age groups (e.g., juvenile-onset and late-onset HD) or different degrees of 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 (letter and category fluency), Symbol Digit Modality Test and Stroop Interference Test. Higher scores indicate better cognitive performance. An extended cognitive assessment includes the following standardised neuropsychological tests: the Hopkins Verbal Learning Test; Trail Making (Parts A & B); Mattis Dementia Rating Scale (optional).

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. Note: **PBA-s** trained site investigators are permitted to administer the PBA-s in place of the UHDRS-Behavioural scale. To gauge an individual's suicidality and risk of harm to self and others, the **CSSRS** can be administered by a rater following a structured interview. This scale was developed in the National Institute of Mental Health Treatment of Adolescent Suicide Attempters Study to assess severity and monitor suicidal events during a treatment period (39). The interview can provide an overall assessment of suicidal ideation as well as behaviour in order to generate a summary measure of suicidality. This rating scale has been used in prior interventional studies for both psychotropic and non-psychotropic compounds over recent years. All personnel involved in this assessment will be informed of the risk indicators and protocols outlined in the REGISTRY SOP for Risk Assessment for harm to self_others.

The **HADS-SIS** combined is a self-report rating scale. The **HADS** offers a brief rating of depression and anxiety symptoms that reflects primarily mood rather than cognitive and somatic symptoms. This commercially available scale has 14 items, 7 measuring anxiety and 7 measuring depression producing separate anxiety and depression sub-scores. Each item is rated on a four-point scale. Individual item and global (summed) depression and anxiety sub-scores will be analysed. The HADS has an advantage over the BDI in that the HADS is less susceptible to confounds from the somatic symptoms in HD. Moreover, in a recent validation study (against the SCAN – Schedule for Clinical Assessment in Neuropsychiatry) by Jenny Keylock from Hugh Rickard's group at the Barberry Centre in Birmingham, UK, the depression sub-scale of the HADS (HADS-D) was found to discriminate maximally between depressed and non-depressed HD patients whereas the BDI-II performed the least satisfactorily of all scales (40).

The **SIS** is a brief rating scale of irritability by self and companion (two separate forms). The scale is composed of 8 items each rated on a four-point scale. Four items are focused on inwardly focused irritability and four items are focused on outward irritability. Individual item and global (summed) inward and outward irritability sub-scores will be analysed as well as a total scale score.

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 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.



6.15.3 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
- local availability of DNA samples
- 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 they 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.

6.15.4 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 QC 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 (41-43).
- All activities and testing will be documented.

6.16 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 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 according to BioRep SOPs (Certificates for each sample document all the processes performed and instruments used accordingly).

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

- One tube of peripheral blood will be collected in a 10 ml yellow topped ACD 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 will be isolated from the blood sample and cryopreserved.
- All activities and testing will be documented according to BioRep SOPs (Certificates for each sample document all the processes performed and instruments used accordingly).

The following process will be performed for the isolation plasma from the blood sample

- Draw blood and insert into 1 x 9.5 ml EDTA tubes.
- Rapid processing of the sample is optimal. Centrifugation (refrigerated centrifuge) is carried out within 30 minutes of blood draw.
- Plasma is aliquotted into sterile cryotubes and put directly into a -80°C freezer.
- Shipping labels and detailed packaging instruction will be provided by BioRep and shipped on dry ice by a courier service.

Genotypic Evaluation – To ensure uniformity of CAG repeat sizing, REGISTRY-HD participants 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.



7 ETHICAL CONSIDERATIONS

7.1.1 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.

7.1.2 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 FHQ. In addition, despite best efforts, it is not humanly possible to exclude with 100% certainty a breach of confidentiality by unauthorised 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 customised to run the bare minimum of network services in order to minimise 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 minimising 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 authorised 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. Localised 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.



7.1.3 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.

7.1.4 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.

7.1.5 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.

7.1.6 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').



8 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 day 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 include 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 (H^2) 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.

8.1 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.

Potential proteomic, neuroinflammatory, endocrine and metabolic markers identified from current ongoing biomarker research initiatives will be further validated using the EHDN plasma samples. Specific *a priori* candidates will then be analysed using longitudinal analyses of samples over specified time intervals (i.e. 12 – 24 months). Any additional screening for new candidate markers will be subject to multiple comparison corrections (e.g. false discovery rate) in assessing the probable statistical and



scientific significance of the results. Changes in each of the laboratory biomarkers identified will be correlated with the clinical phenotypic data using multi-variate assessments.

8.2 Forms and data handling

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, QC 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.

8.3 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 EHDN, the investigators and the IRB will agree upon such amendments prior to implementation.



9 APPENDIX A: REGISTRY STEERING COMMITTEE

As of 01 November, 2009 the REGISTRY Steering Committee includes the following EHDN members:

- A.-C. Bachoud-Levi, MD PhD** (Hôpital Henri Mondor, Créteil)
- A. R. Bentivoglio, MD** (Università Cattolica del Sacro Cuore, Rome)
- I. Biunno, PhD** (BioRep, Milan)
- R. Bonelli, MD** (Vienna, Austria)
- J. M. Burgunder, MD** (Neurologische Klinik des Inselspitals, Bern, Switzerland)
- S. Dunnett, DSc** (Cardiff University, United Kingdom)
- J. Ferreira, MD** (Centro de Estudos Egas Moniz, Lisbon, Portugal)
- O. Handley, PhD** (University College London, United Kingdom)
- A. Heiberg, MD, PhD** (Rikshospitalet, Oslo, Norway)
- T. Illmann** (2mt, Germany)
- S. Illarionov, MD** (Russian Academy of Medical Sciences, Moscow, Russia)
- G. B. Landwehrmeyer, MD** (Principle Investigator, University of Ulm, Germany)
- J. Levey** (EHDN, Paris, France)
- J. Nielsen, MD** (University Hospital of Copenhagen, Copenhagen, Denmark)
- H. Padieu** (EHDN, Paris, France)
- S. Pålhagen, MD** (Karolinska Institute, Lund, Sweden)
- M. Päiväranta, MD** (Turku University, Finland)
- R.A.C. Roos, MD** (Leiden University Medical Centre (LUMC), Leiden, Netherlands)
- M. Ramos-Arroyo MD, PhD** (Dept. of Medical Genetics, Pamplona, Spain)
- S. Tabrizi, MD PhD** (Co-Investigator; University College London, United Kingdom)
- T. Uhrova, MD** (Centrum Extrapiramidových Onemocnění, Prague, Czech Republic)
- D. van Kammen, MD** (Chief Medical Officer, CHDI Foundation, Inc.)
- M. van Walsem, MSc** (EHDN, Rikshospitalet, Oslo, Norway)
- W. Vandenberghe, MD** (Universitair Ziekenhuis Gasthuisberg, Leuven, Belgium)
- C. Verellen-Dumoulin, MD** (UCL-St Luc, Brussels, Belgium)
- J. Zaremba, MD** (Warsaw, Poland)



10 APPENDIX B INFORMATION AND CONSENT FORMS

10.1 Participant Information Sheet (New REGISTRY-HD Participants)

Name of study: **REGISTRY – an observational study of the European Huntington's disease Network (EHDN)**

Dear Participant,

You are either suffering from Huntington's disease (HD) or you belong to an HD family. The clinical team 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 healthcare 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 healthcare 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, scientists and organisations for families affected by HD to collaborate in support of research 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 the CHDI Foundation, Inc., a private, not-for-profit American research organisation. For more information about CHDI, please visit the website at www.chdifoundation.org.

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 regular intervals (e.g. yearly).

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 stored under a pseudonym in an electronic database and
- your consent to regular (e.g. yearly) follow-up visits



Any additional research components described below are optional and require your explicit consent by checking the box 'YES' or 'NO' in the consent form. The optional components are

- permission to be contacted in-between visits, ([Optional component 1](#)),
- donation of blood and urine for studies to identify genetic modifiers of HD and to establish and validate biological markers for HD ([Optional component 2](#)),
- analysis of a blood sample for the HD mutation ([Optional component 3](#)),
- completion of a family history questionnaire ([Optional component 4](#)),
- collection of retrospective clinical data, ([Optional component 5](#))
- participation in novel assessments ([Optional component 6](#)), and
- videotaping of assessments for research/teaching purposes ([Optional component 7](#)).

You may choose 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),
- provide you with updates on REGISTRY or
- 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 regularly (e.g. yearly) 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 pseudonymised and stored centrally in a biorepository devoted to the safe storage and handling of biomaterials. BioRep S.r.l. is an independent organisation based in Milan, Italy, that offers biorepository services to public and private research institutes, to the highest standards of quality and safety. For more information on BioRep, please visit the website at www.biorep.it.

Access to biosamples will be granted to researchers whose proposals were approved by a panel of experienced scientists and clinicians who form the Scientific and Bioethical Advisory Committee (SBAC) 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 allowing 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 experience 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 (e.g. yearly), so there is no risk of developing an anaemia.

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.

Optional component 5: Retrospective clinical data

We would like to ask you to consider giving permission to use information from your past clinical assessments that were performed before your participation in REGISTRY. Many people taking part in REGISTRY have undergone regular assessments for a number of years. The information held within these past clinical evaluations may help us to understand the course of HD better.

Optional component 6: Novel assessments

A number of novel assessments (e.g. questionnaires, interviews, rating scales) may help us to understand more about the onset, course and treatment of Huntington's disease. We need to collect more data on each assessment in order to know whether they should be used in the design of future research and clinical care practices.

We would like to ask you to consider taking part in these novel assessments. The novel assessments cover a wide range of areas (e.g. information on your well-being, your quality of life, and particular signs and symptoms you may be feeling) and you may be approached to take part. The overall duration of the novel assessments together with the standard REGISTRY assessments should not exceed 2.5 hours. You can decide whether you want to do the additional assessments or not during your visit.

Optional component 7: Videotaping

For certain assessments included in REGISTRY, you may also be asked to be videotaped. The videotapes will be visible for a restricted number of EHDN members (e.g. experienced physicians, for consultation purposes, physicians in training) for quality control, research and training purposes only. The recordings will be transmitted via secure internet connection and will be stored on the REGISTRY server in a pseudonymised form.

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. On your request every link between your stored data and your person can be permanently deleted (for details see **Information regarding data processing, data protection and data security, point 'E'**)

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, authorised individuals (e.g. the sponsor, the university) are permitted to review your local medical records.

If individuals authorised 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.

European 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.

A. 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.

B. 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.

C. 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. EHDN staff (Language area coordinators acting as monitors, monitors based in Central Coordination): EHDN 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. EHDN staff can only view and use pseudonymised data entered on the EHDN network. For the purpose of data control, EHDN staff ('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 local medical records. Monitors/auditors are bound by medical confidentiality.

4. Authorised researchers (scientist/clinicians): Scientists/clinicians who are involved in HD research can apply to the Scientific and Bioethical Advisory Committee (SBAC) of EHDN (a group of experienced clinicians and scientists) for authorisation to obtain access to the data base. Authorised researchers can only view coded data. To ensure the highest degree of confidentiality pseudonyms are recoded before the data bank is made available to authorised researchers. Thereby it is guaranteed that all publications reporting on the findings of authorised research exclusively use anonymised data report format (i.e. not even using the pseudonym).

5. System administrators: In order to safeguard the EHDN 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.

D. 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').

E. How long are my data stored for?

All data will be stored as entered:

- until you withdraw your participation and request the anonymisation of your data
- until 10 years after an efficient therapy for HD has been established
- a maximum period of 60 years (2 generations + 10 years), or
- up to a maximum of 10 years after the project activities have stopped.

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



10.2 Participant Consent Form (New REGISTRY-HD Participants)

Name of study: **REGISTRY – an observational study of the European Huntington's 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 I had the opportunity to ask questions and obtain answers 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:

I agree to participate in the standard REGISTRY assessment and receive regular (e.g. yearly) follow-up visits. My decisions to participate in each of the optional components are provided below:

Optional component 1: 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

Optional component 2: 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 at each visit (e.g. yearly) 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 BioRep S.r.l., a central biorepository located in Milan (Italy) for the next two generations (60 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

Optional component 3: 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

Optional component 4: 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.

Yes No

Optional component 5: Retrospective clinical data

I agree that my past clinical data generated at my study site can be stored as part of the REGISTRY database.

Yes No

Optional component 6: Novel assessments

I agree to receive information about the novel assessment battery and to participate in the development of novel assessments.



10.3 Participant Information Sheet (Existing REGISTRY-HD Participants)

Name of study: **REGISTRY – an observational study of the European Huntington's disease Network (EHDN)**

Dear Participant,

You are already a participant of REGISTRY and 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. To date, you have consented to participating in REGISTRY, which means that with your permission, we carry out a thorough standard examination and the documentation of the data obtained during your clinical examination stored under a pseudonym on an electronic database and your consent to regular (e.g. yearly) follow-up visits. You may or may not have consented to a number of optional components, including the collection of family history information, the collection of blood and urine for biomarker and genetic modifier studies, HD gene testing for research purposes and permission to be contacted between visits.

Since you enrolled to take part in this study, REGISTRY has adopted additional optional components. We would like to invite you to take part in any or all of the following optional components:

- collection of retrospective clinical data, ([Optional component 1](#))
- participation in novel assessments ([Optional component 2](#)), and
- videotaping of assessments for research/teaching purposes ([Optional component 3](#)).

Optional component 1: Retrospective clinical data

We would like to ask you to consider giving permission to use information from your past clinical assessments that were performed before your participation in REGISTRY. Many people taking part in REGISTRY have undergone regular assessments for a number of years. The information held within these past clinical evaluations may help us to understand the course of HD better.

Optional component 2: Novel assessments

A number of novel assessments (e.g. questionnaires, interviews, rating scales) may help us to understand more about the onset, course and treatment of Huntington's disease. We need to collect more data on each assessment in order to know whether they should be used in the design of future research and clinical care practices.

We would like to ask you to consider taking part in these novel assessments. The novel assessments cover a wide range of areas (e.g. information on your well-being, your quality of life, and particular signs and symptoms you may be feeling) and you may be approached to take part. The overall duration of the novel assessments together with the standard REGISTRY assessments should not exceed 2.5 hours. You can decide whether you want to do the additional assessments or not during your visit.

Optional component 3: Videotaping.

For certain assessments included in REGISTRY, you may also be asked to be videotaped. The videotapes will be visible for a restricted number of EHDN members (e.g. experienced physicians, for consultation purposes, physicians in training) for quality control, research and training purposes only. The recordings will be transmitted via secure internet connection and will be stored on the REGISTRY server in a pseudonymised form.

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. On your request every link between your stored data and your person can be permanently deleted (for details see **Information regarding data processing, data protection and data security, point 'E'**).

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, authorised individuals (e.g. the sponsor, the university) are permitted to review your local medical records.

If individuals authorised 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.

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

A. 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.

B. 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.

C. 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. EHDN staff: EHDN 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. EHDN staff can only view and use pseudonymised data entered on the EHDN network. For the purpose of data control, EHDN staff ('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 local medical records. Monitors/auditors are bound by medical confidentiality.

4. Authorised researchers (scientist/clinicians): Scientists/clinicians who are involved in HD research can apply to the Scientific and Bioethical Advisory Committee (SBAC) of EHDN (a group of experienced clinicians and scientists) for authorisation to obtain access to the data base. Authorised researchers can only view coded data. To ensure the highest degree of confidentiality pseudonyms are recoded before the data bank is made available to authorised researchers. Thereby it is guaranteed that all publications reporting on the findings of authorised research exclusively use anonymised data report format (i.e. not even using the pseudonym).

5. System administrators: In order to safeguard the EHDN 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.

D. 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').

E. How long are my data stored for?

All data will be stored as entered:

- until you withdraw your participation and request the anonymisation of your data
- until 10 years after an efficient therapy for HD has been established
- a maximum period of 60 years (2 generations + 10 years), or
- up to a maximum of 10 years after the project activities have stopped.

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



10.4 Participant Consent Form (Existing REGISTRY-HD Participants)

Name of study: **REGISTRY – an observational study of the European Huntington’s 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 I had the opportunity to ask questions and obtained answers 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:

Optional component 1: Retrospective clinical data

I agree that my past clinical data generated at my study site can be stored as part of the REGISTRY database.

Yes No

Optional component 2: Novel assessments

I agree to receive information about the in the novel assessment battery and to participate in the development of novel assessments.

Yes No

Optional component 3: Videotaping

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

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 (e.g. EHDN monitors, regulatory authorities) 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



EUROPEAN HUNTINGTON'S DISEASE NETWORK

.....
Name of Legal Representative (if applicable) Signature of the Legal Representative Place, date

.....
Name of Consultee/Witness (optional) Signature of the Consultee/Witness Place, date

.....
Name of Person Obtaining Consent Signature of Person Obtaining Consent Place, date
(Printed Name and Title)

REGISTRY PSEUDONYM:



10.5 Participant Information Sheet (REGISTRY-COMPANIONS)

Name of study: **REGISTRY – an observational study of the European Huntington's disease Network (EHDN)**

Dear Companion,

You are accompanying/assisting somebody from a family affected by Huntington's disease (HD). Your 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 the participant 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 regularly (e.g. yearly) for the follow-up visit.

The results of your companion's examinations will be stored under a pseudonym on 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.

There is a further, optional research component described below. This requires your explicit consent by checking the box 'YES' or 'NO' in the consent form.

Optional component 1: Novel assessments

A number of novel assessments (e.g. questionnaires, interviews, rating scales) may help us to understand more about the onset, course and treatment of Huntington's disease. We need to collect more data on each of assessment in order to know whether they should be used in the design of future research and clinical care practices.

We would like to ask you to consider taking part in these novel assessments. The novel assessments cover a wide range of areas (e.g. information on your well-being, your quality of life, and particular signs and symptoms your companion may be feeling) and you may be approached to take part. You can decide whether you want to do the additional assessments or not during your visit.

REGISTRY is a study conducted by the European Huntington's Disease Network (EHDN). EHDN is a scientific network of physicians, scientists and organisations for families affected by HD to collaborate in support of research committed to HD. The EHDN is supported by the CHDI Foundation, Inc., a private, not-for-profit American research organisation. For more information about CHDI, please visit the website at www.chdifoundation.org. 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. 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. Withdrawal from the study will not affect the care given to you or your



companion. On your request every link between your stored data and your person can be permanently deleted (for details see **Information regarding data processing, data protection and data security, point 'E'**).

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, authorised individuals (e.g. the sponsor, the university) are permitted to review your local medical records.

If individuals authorised 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.

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

A. 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.

B. 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.

C. 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. EHDN staff: EHDN 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. EHDN staff can only view and use pseudonymised data entered on the European-HD network. For the purpose of data control, EHDN staff ('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 local medical records. Monitors/ auditors are bound by medical confidentiality.

3. Authorised researchers (scientist/clinicians): Scientists/clinicians who are involved in HD research can apply to the Scientific and Bioethical Advisory Committee (SBAC) of EHDN (a group of experienced clinicians and scientists) for authorisation to obtain access to the data base. Authorised researchers can only view coded data. To ensure the highest degree of confidentiality pseudonyms are recoded before the data bank is made available to authorised researchers. Thereby it is guaranteed that all publications reporting on the findings of authorised research exclusively use anonymised data report format (i.e. not even using the pseudonym).

4. System administrators: In order to safeguard the EHDN 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.

D. 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').

E. How long is my and my companion's data stored for?

All data will be stored as entered:

- until you withdraw your participation and request the anonymisation of your data
- until 10 years after an efficient therapy for HD has been established
- a maximum period of 60 years (2 generations + 10 years), or
- up to a maximum of 10 years after the project activities have stopped.

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



10.7 Participant Information Sheet (New REGISTRY-CONTROL)

Name of study: **REGISTRY – an observational study of the European Huntington's disease Network (EHDN)**

Dear Participant,

You are a person without a HD family history. We would like to invite you to be interviewed and examined by an experienced clinician. In other words, at each study visit, your physical and mental ability will be assessed; these examinations will be very similar to the standardised assessments undertaken by your companion and it may be that you are already familiar with them from previous consultations with your companion. In addition, you will be asked to complete questionnaires assessing your wellbeing.

You can also 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) at each visit (e.g. yearly). To make sure that your own state of health (especially 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.

The results of your interview and of your clinical assessments will be stored under a pseudonym on 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 standard interview and examination and the documentation of the data obtained during your clinical examination in an electronic database and two optional components which you may wish to consider.

Any additional research components described below are optional and require your explicit consent by checking the box 'YES' or 'NO' in the consent form. The optional components are

- the donation of blood and urine for studies to identify genetic modifiers of HD and to establish and validate biological markers for HD,
- participation in novel assessments

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

Optional Component 1: Donation of blood and urine for studies to identify genetic modifiers of HD and to establish and validate biological markers for HD

Donating blood to allow scientific studies to find genes helps us understand their influence on 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 pseudonymised and stored centrally in a biorepository devoted to the safe storage and handling of biomaterials. BioRep S.r.l. is an independent organisation based in Milan, Italy, that offers biorepository services to public and private research institutes, to the highest standards of quality and safety. For more information on BioRep, please visit the website at www.biorep.it.

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 experience 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 (e.g. yearly), so there is no risk of developing an anaemia.

Optional component 2: Novel assessments

A number of novel assessments (e.g. questionnaires, interviews, rating scales) may help us to understand more about the onset, course and treatment of Huntington's disease. We need to collect more data on each assessment in order to know whether they should be used in the design of future research and clinical care practices.

We would like to ask you to consider taking part in these novel assessments. The novel assessments cover a wide range of areas (e.g. information on your well-being, your quality of life) and you may be approached to take part. The overall duration of the novel assessments together with the standard REGISTRY assessments should not exceed 2.5 hours. You can decide whether you want to do the additional assessments or not during your visit.

REGISTRY is a study conducted by the European Huntington's Disease Network (EHDN). EHDN is a scientific network of physicians, scientists and organisations for families affected by HD to collaborate in support of research 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. 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. EHDN is supported by the CHDI Foundation, Inc., a private, not-for-profit American research organisation. For more information about CHDI, please visit the website at www.chdifoundation.org.

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. On your request every link between your stored data and your person can be permanently deleted (for details see **Information regarding data processing, data protection and data security, point 'E'**).

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, authorised individuals (e.g. the sponsor, the university) are permitted to review your local medical records. If individuals authorised 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.

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

A. 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.

B. 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.

C. 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. EHDN staff: EHDN 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. EHDN staff can only view and use pseudonymised data entered on the European HD network. For the purpose of data control, EHDN staff ('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 local medical records. Monitors/auditors are bound by medical confidentiality.

4. Authorised researchers (scientist/clinicians): Scientists/clinicians who are involved in HD research can apply to the Scientific and Bioethical Advisory Committee (SBAC) of EHDN (a group of experienced



clinicians and scientists) for authorisation to obtain access to the data base. Authorised researchers can only view coded data. To ensure the highest degree of confidentiality pseudonyms are recoded before the data bank is made available to authorised researchers. Thereby it is guaranteed that all publications reporting on the findings of authorised research exclusively use anonymised data report format (i.e. not even using the pseudonym).

5. System administrators: In order to safeguard the European 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.

D. 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').

E. How long are my data stored for?

All data will be stored as entered:

- until you withdraw your participation and request the anonymisation of your data
- until 10 years after an efficient therapy for HD has been established
- a maximum period of 60 years (2 generations + 10 years), or
- up to a maximum of 10 years after the project activities have stopped.

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



10.8 Participant Consent Form (New REGISTRY-CONTROL Participant)

Name of study: **REGISTRY – an observational study of the European Huntington’s 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

I had the opportunity to ask questions and obtain answers 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 participant information and of the consent form.

I agree to participate in the standard REGISTRY (CONTROL) assessment and receive regular (e.g. yearly) follow-up visits. My decisions to participate in each of the optional components are provided below:

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

Optional component 1: 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 (60 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

Optional component 2: Novel assessments

I agree to receive information about the novel assessment battery and to participate in the development of novel assessments.

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 (e.g. EHDN monitors, regulatory authorities) 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



.....
Name of Person Obtaining Consent
Printed Name and Title

.....
Signature of Person Obtaining Consent

.....
Place, date

REGISTRY (CONTROL) PSEUDONYM:



10.9 Participant Information Sheet (Existing REGISTRY-CONTROL Participants)

Name of study: **REGISTRY – an observational study of the European Huntington's disease Network (EHDN)**

Dear Participant,

You are already a participant of REGISTRY. To date, you have consented to participating in REGISTRY, which means that with your permission, we carry out a thorough standard examination and the documentation of the data obtained during your clinical examination stored under a pseudonym on an electronic database and your consent to regular (e.g. yearly) follow-up visits. You may or may not have consented to an optional components donate of blood and urine for biomarker and genetic modifier studies.

Since you enrolled to take part in this study, REGISTRY has adopted an additional optional component. We would like to invite you to take part in the following:

- participation in novel assessments (Optional component 1)

Optional component 1: Novel assessments

A number of novel assessments (e.g. questionnaires, interviews, rating scales) may help us to understand more about the onset, course and treatment of Huntington's disease. We need to collect more data on each assessment in order to know whether they should be used in the design of future research and clinical care practices.

We would like to ask you to consider taking part in these novel assessments. The novel assessments cover a wide range of areas (e.g. information on your well-being, your quality of life) and you may be approached to take part. The overall duration of the novel assessments together with the standard REGISTRY assessments should not exceed 2.5 hours. You can decide whether you want to do the additional assessments or not during your visit.

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. On your request every link between your stored data and your person can be permanently deleted (for details see **Information regarding data processing, data protection and data security, point 'E'**).

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, authorised individuals (e.g. the sponsor, the university) are permitted to review your local medical records.

If individuals authorised 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.



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

A. 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.

B. 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.

C. 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. EHDN staff: EHDN 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. EHDN staff can only view and use pseudonymised data entered on the EHDN network. For the purpose of data control, EHDN staff ('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 local medical records. Monitors/auditors are bound by medical confidentiality.

4. Authorised researchers (scientist/clinicians): Scientists/clinicians who are involved in HD research can apply to the Scientific and Bioethical Advisory Committee (SBAC) of EHDN (a group of experienced clinicians and scientists) for authorisation to obtain access to the data base. Authorised researchers can only view coded data. To ensure the highest degree of confidentiality pseudonyms are recoded before the data bank is made available to authorised researchers. Thereby it is guaranteed that all publications reporting on the findings of authorised research exclusively use anonymised data report format (i.e. not even using the pseudonym).



5. System administrators: In order to safeguard the EHDN 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.

D. 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').

E. How long are my data stored for?

All data will be stored as entered:

- until you withdraw your participation and request the anonymisation of your data
- until 10 years after an efficient therapy for HD has been established
- a maximum period of 60 years (2 generations + 10 years), or
- up to a maximum of 10 years after the project activities have stopped.

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



10.10 Participant Consent Form (Existing REGISTRY-CONTROL Participants)

Name of study: **REGISTRY – an observational study of the European Huntington’s 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 I had the opportunity to ask questions and obtained answers 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:

Optional component 1: Novel assessments

I agree to receive information about the in the novel assessment battery and to participate in the development of novel assessments.

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 (e.g. EHDN monitors, regulatory authorities) 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

.....
Name of Person Obtaining Consent
(Printed Name and Title)

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Signature of Person Obtaining Consent Place, date

REGISTRY (CONTROL) PSEUDONYM

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10.11 Family member (Invitation letter)

Invitation to take part in REGISTRY, a large European study into Huntington's disease

We are approaching you because we understand you have a relative who has a family history of Huntington's disease (HD). This information sheet has been given to you by a relative who already participates in REGISTRY and was kind enough to give it to you on our request.

REGISTRY is a study conducted by a network of clinicians and scientists from across Europe. The aims of the study are to (i) improve the understanding of HD, (ii) improve management and treatment options for HD.

In addition, a major goal of REGISTRY is to determine how environmental and genetic factors may influence the onset and course of the disease and also how it differs in families. We hope that obtaining this information will assist us in determining more effective treatment strategies. Therefore, as the organisers of REGISTRY, we are informing you about this study to see if you would like to take part.

What is REGISTRY?

REGISTRY is a long-term, observational study that has the aim of gathering a large amount of reliable data on the symptoms and course of HD. As the disease has not yet been fully characterised, this is essential for informing treatment strategies.

Who sponsors REGISTRY?

The study is sponsored by a private American Foundation (CHDI Foundation, Inc.).

Who can take part?

If you are a family member of someone who has HD (even if you do not carry the gene yourself) or have HD you are eligible to take part in REGISTRY. Spouses and carers can also contribute information and biosamples to the study.

I would like to have more information on REGISTRY and the European-HD Network – where do I find more details?

Please visit the Euro-HD website (<http://www.euro-hd.net>) or if you would prefer direct contact, get in touch with PI NAME at the study which enrolled your relative. PI NAME can be reached at xxxx (phone) or xxx (fax); the postal address is (xxx, xxx). If you would like to have information on other participating study sites potentially more conveniently located for you please get in touch with the European-HD Network language area coordinator (xxx, Tel: xxx, Email: xxx, Fax: xxx, Address). Details of the nearest participating centre can also be found on the website under Network> Locations.

We would be extremely grateful if you would consider participating in this research. **We wish to make it clear that your participation in our study is voluntary and a refusal to take part or a decision to withdraw at any time would not affect current or future medical treatment.**



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