Scientific Strategic Plan

for the European Huntington's Disease Network

2011-2015

History and Mission of EHDN

Established in 2004, the European Huntington's Disease Network (EHDN) is a not-for-profit scientific organisation focused on Huntington's disease (HD). It gathers researchers, clinicians and other healthcare providers from various disciplines, as well as individuals and families affected by HD, all working together towards a common aim: **to find a cure for HD.**

In practice, EHDN serves as a platform for clinicians, scientists, research centres, HD clinics and organisations for families affected by HD to collaborate in support of preclinical and clinical research on HD.

The main mission of EHDN is *to advance knowledge of Huntington's disease by supporting scientific and clinical efforts to develop and test therapeutic interventions that will improve the quality of life of people with Huntington's disease*.

In simple terms this means…

- **SCIENCE: to advance scientific and clinical knowledge of Huntington's disease**
- **TREATMENT: to develop and test efficacious therapeutic interventions**
- **CARE: to improve the health status of patients, at-risk individuals and family members of people with Huntington's disease**

EHDN is also committed to the **principles** of

- open and full scientific communication
- broad **sharing of scientific data**
- **collaborative** planning and implementation of scientific projects and clinical studies
- compliance with applicable **good clinical practice** in all scientific projects and clinical studies
- peer review
- **prompt publication of all valid results** of scientific enquiry
- full and open disclosure of potential conflicts of interest
- democratic governance of its organisation and activities

- **working with other professional organisations**, government and industry sponsors, and lay organisations, and
- recognition and protection of the interests of people with Huntington's disease and their families.

The history of EHDN dates back to the year 1999 and to the roots of the European Huntington's Disease Initiative (EHDI) Study Group. Researchers from eight European countries (Austria, France, Germany, Italy, the Netherlands, Poland, Spain and Switzerland) conceived and conducted a large, multinational, phase III, double-blinded clinical trial of riluzole in HD patients [Landwehrmeyer GB et al. 2007]. The study included 537 adult HD patients, who were randomised to treatment with riluzole or placebo for three years. Patients were included at 44 centres across Europe between November 1999 and May 2001. The last patient terminated the study protocol in July 2004. EHDI found no evidence for the efficacy of riluzole in HD at the tested dose. Nevertheless, the study illustrated the feasibility of conducting large-scale, long-term clinical trials in HD and the merits of establishing a network focused on HD research in Europe. EHDI was initiated by academic members from eight European countries and funded by a pharmaceutical company, Sanofi-Aventis, the manufacturer of riluzole.

This study built the foundations of the European HD Network: the investigators who had participated in the EHDI trial became the founder members of EHDN and the clinics which had recruited the trial subjects became the first EHDN Study Sites. The idea of an European HD Network was kick-started at the Gordon Research Conference in Il Ciocco, Italy, in May 2003. Private American donors, that also support HD research through the CHDI Foundation, became interested in the project and decided to sponsor EHDN in its first ten years of activity.

Context of the Scientific Strategic Plan

The proposal to develop a Scientific Strategic Plan arrives at the opportune moment when EHDN has grown into a well-organised and consolidated European-based network which is able to design and conduct high-quality preclinical and clinical research studies as well as to offer a network of clinical centres for HD patients.

This first Strategic Plan aims to improve the quality and efficiency of research activities within EHDN and to refocus them on EHDN's main mission. Starting from an overview of the research activities carried out from 2004 to 2010 and the achievements of the Network to date, the Strategic Plan represents an explicit move from a well-developed and consolidated organisation to a structure with scientific output. It is based on a move from an initially promoted bottom-up decision strategy **to a more explicit top-down approach**. This has provided not only an accurate analysis of the current state of EHDN research, but also initiated the discussion on what is the target state and how to get there. This Strategic Plan is intended to close the gaps between current state and target state, as well as to discuss and propose tools to monitor the future progress of the Network.

Having a consolidated Network which provides the required structure , it was considered that this was the right moment to guide EHDN's activities, especially in view of the upcoming implementation of the global HD cohort study Enroll-HD, which promotes a fusion of the European and the North American and Australia studies with the integration of the new Latin American HD Network. In addition, many compounds in the drug pipeline are expected to shortly advance from the preclinical to the clinical stage, and this constitutes an additional demand for the Network.

Opportunities and Challenges

- Internal
  - Opportunities / Strengths
    - Well-developed and large Network
    - Highly motivated and knowledgeable collaborators
    - Substantial human and material resources and a stable source of funding
    - Free to investigate all aspects of HD
  - Challenges / Weaknesses
    - Multiple countries, languages and regulations
    - Combine individual interests to the main goals of the Network
    - Source of funding has a limited lifespan

- External
  - Opportunities
    - Become a leader in HD research
    - Define the research and regulatory standards that will shape the development of HD therapeutics
    - Narrow the gaps between basic researchers, clinicians, pharmaceutical industry and patients
  - Challenges
    - High expectations for therapeutic results

With 1,117 regular members and 132 associate members from 37 countries by 31-Dec-2010 [Landwehrmeyer GB 2010], EHDN is a large and well-developed Network with highly motivated voluntary collaborators and knowledgeable experts from different fields. Members are mostly professionals active in the care of people affected by HD. The second

largest group of members consists of scientists conducting research on HD, the third largest by family members linked to HD support associations.

In addition to this valuable human resource, EHDN has solid material resources and a stable source of funding provided by the donors to the CHDI Foundation. CHDI has been providing financial support to EHDN since 2004, enabling and accelerating the conduct of research related to all different aspects of HD, from genetic testing in premanifest gene carriers to provision of care at advanced stages, from evaluation of candidate drugs in the laboratory to developing clinical tools to conduct high-quality and conclusive clinical trials in patients. However, this source of funding is external to the Network and is not endless.

The largest observational study of EHDN is REGISTRY. By 31-Dec-2010, there were 127 study sites from 19 countries enrolled in REGISTRY. As HD is a rare disease, the need to enrol a high number of potential study participants is beyond debate. However, this also imposes challenges for management, organisation and logistics arising from the need to recruit patients in different countries, each having its own language, culture, and national regulations on the approval and conduct of clinical trials.

With the exception of studies fully conducted by EHDN (e.g. REGISTRY), all other studies result from the combination of areas of interest of individual research groups and projects developed at single centres, fostered by the facilitating conditions offered by the Network (e.g. through the working groups). Combining these interests and resources is another challenge for the Network.

At the international level, EHDN is in the best position to become a leader in HD research and to define research and regulatory standards that will shape the development of HD therapeutics. This is obviously paired with high expectations, from both the research and clinical community and HD families, for therapeutic results in the form of effective and marketable drugs. As a multidisciplinary network, EHDN also has the potential to narrow the gaps between basic researchers, clinicians, pharmaceutical companies and patients. In

addition, EHDN may set an example for organisations focusing on other neurodegenerative disorders, such as Alzheimer's disease and Parkinson's disease.

Development of the Scientific Strategic Plan

The Executive Committee (EC) of EHDN proposed the development of this Scientific Strategic Plan in December 2010. A Strategic Plan Team was established, composed of Joaquim Ferreira, Bernhard Landwehrmeyer, Jamie Levey and Tim McLean. Joaquim Ferreira was appointed EHDN's Scientific Director in September 2010. He was in charge of leading the process and developing the document. A Strategic Planning Advisory Committee composed of Joaquim Ferreira, Bernhard Landwehrmeyer, Jean-Marc Burgunder, Raymund Roos, Ralf Reilmann, Sarah Tabrizi, Anne-Catherine Bachoud-Lévi and Michael Orth was created to give scientific advice through the process.

The Strategic Plan Development Process took place in three stages:

i. Overview of current and past EHDN research activities from 2004 to December 2010

   These data were collected by Joaquim Ferreira and presented to the EHDN EC and at webinars on January 31st and February 3rd 2011, which were attended by Lead Facilitators of EHDN Working Groups (WGs), members of the Scientific and Bioethics Advisory Committee (SBAC) and Principal Investigators (PIs) of the REGISTRY Study.

ii. Discussion and draft

   A Strategic Plan Meeting took place in March 2011 in London. Attendees included the WG Lead Facilitators, SBAC members and REGISTRY's PIs. WG Lead Facilitators were asked to provide information concerning the WG achievements to date, including publications and assessments developed, and to project objectives and actions for 2011-2015. Additional discussions took place at the Executive Committee (EC) meeting in Stockholm in May 2011 and during the regular EC calls in August and September.

iii. Review and approval

   The final version of the Strategic Plan was approved by the EHDN Executive Committee in October 2011.

Guiding principles

- In accordance with EHDN mission
- Realistic proposals supported by the current EHDN structure
- Incorporates the characteristics that favoured the success of EHDN foundation and development: The balance between
  - robust network
  - members' own areas of research interest
  - focused research
  - dynamic governance
  - generosity/voluntary contribution

It is fundamental that the principles guiding the development of this Strategic Plan are in accordance with EHDN's mission. Proposed actions and activities should be realistic, and the current EHDN structure should be appropriate to support them. They should profit from the characteristics that favoured the success of EHDN foundation and development, i.e. the variety of expertise in different specialities from healthcare, basic and clinical research in several European countries. Furthermore, the Strategic Plan should provide a balance between a robust network, where members have the opportunity to pursue their own areas of research interest, on the one side and focused and objective strands of research on the other side. The equilibrium should also take into account that the majority of active EHDN members collaborate on a voluntary basis.

Overview of main research activities from 2004-2010

The presentation of the main activities performed by the Network is based on what we describe as "research functional units". This classification does not follow a predefined structural division of the Network but only a pragmatic organisational proposal for this purpose.

Research functional units

- **Working groups**
- **Research projects:**
  - **SBAC approved (including REGISTRY)**
  - **Seed fund projects**
- **Clinical studies**
  - **REGISTRY study**
  - **Clinical trials**
  - **EHDN related studies:**
    - **TRACK-HD**

Working Groups

Working Groups are EHDN's functional units for conducting research. There are currently 21 Working Groups, listed below:

1. Advanced HD (Lead Facilitator: Sophie Duport)
2. Behavioural Phenotype (David Craufurd)
3. Biological Modifiers and Neuroprevention (Christian Neri and Gillian Bates)
4. Biomarkers (Maria Björkqvist and Sarah Tabrizi [LF 2004 - 2010])
5. Brain and Tissue Banking (Justo García de Yébenes)
6. Cognitive Phenotype (Anne-Catherine Bachoud-Lévi and Jennifer Thompson)
7. Environmental Modifiers (Kaye Trembath, Martin Delatycki and Monica Busse)
8. Functional Ability (Aileen Ho and Jim Pollard)
9. Genetic Testing and Counselling (Marina Frontali, Rhona MacLeod and Aad Tibben)
10. Genetic Modifiers (Lesley Jones)
11. Health Economics (Bernhard Landwehrmeyer and Reinhold Kilian)
12. Imaging (Jan Kassubek)
13. Juvenile HD (Oliver Quarrell)
14. Motor Phenotype (Raymund Roos, Peter Kraus and Ralf Reilmann)
15. Neuroprotective Therapy (Joaquim Ferreira and Ralf Reilmann)
16. Physiotherapy (Monica Busse and Lori Quinn)
17. Quality of Life (Christiane Lohkamp and Aileen Ho)
18. Standard of Care (Daniela Rae)
19. Surgical Approaches (Anne Rosser and Stephen Dunnett)
20. Symptomatic Research and Therapy (Josef Priller)
21. Young Adults (Ruth Sands, Michael Orth and Åsa Petersen)

In addition to their function in planning and conducting research on different aspects of HD, the Working Groups provide a platform for facilitating communication between their members. Many of the Working Groups include not only experts but also people affected by HD and representatives of HD lay associations from different countries. The WGs present different levels of activity, and they cover almost the entire spectrum of HD topics, ranging from basic research to topics related to clinical practice and clinical trials. When we consider

the main topics covered by the Working Groups, it is recognised that there are overlaps between some of them, both in theoretical and in a practical sense. It is also accepted that the interactions and collaborations between the Working Groups are limited and can be improved.

There are a number of research and non-research projects ongoing, the majority of which are without full funding. Although the Working Groups have been the driving force in the development of specific research projects, they may also facilitate other research projects evolving from single centres. In general, the main activities of the Working Groups often reflect areas of interest of active members and/or research opportunities. The objectives of the Working Groups are ambitious, but a dissociation between these and the WG capabilities may be eventually observed. This includes the availability of human resources and funds as well as the compliance of objectives with EHDN's mission and their expediency in the context of preparation for clinical trials.

Several Working Groups have been working on the development of new HD-specific rating scales as well as on the improvement of existing ones. The goal is to develop rating scales that are sensitive, reliable and validated for assessing symptoms of HD in the different domains (behavioural, cognitive, functional, motor, physical, etc) and in all disease stages, including the pre-motor manifest stage and juvenile HD.

Research projects

Overview to December 2010

From 2004 to 2010, EHDN approved 73 research projects designed by its members, of which 14 have been concluded, eight scientific papers have been published (Appendix 1) and nine manuscripts have been submitted for publication or are in preparation. A list of all approved projects is provided in Appendix 2. These projects are either seed fund projects resulting from WG activities, requests to mine the data collected through REGISTRY or reflect research activities being carried out at single centres or by single researchers.

Any EHDN member may propose a research project (data mining study or seed fund project). Seed fund projects currently need endorsement by a Working Group. Project applications are submitted electronically via the EHDN web portal. The application process is described at http://www.euro-hd.net/html/projects/proposals. Proposals are first reviewed by the Scientific and Bioethics Advisory Committee (SBAC). The SBAC's recommendations are then forwarded to the Executive Committee, with whom the final decision regarding endorsement of an application rests. The SBAC, working with the Central Coordination, has improved the procedures for the submission, the processing time and the administration of proposals. A SOP was adopted and the time from project submission to contract signing and data/sample transfer is improving through better communication and regular practice.

Seed fund projects

This scheme is intended to facilitate the provision of limited funds to investigators for pilot or small studies that are needed in order to conduct exploratory or preliminary studies before application for funding of larger studies or application for grants from other organisations. Studies funded through this scheme should result in conclusive answers to the hypothesis underlying the study.

Fourteen seed fund projects have been submitted, of which half are WG-related projects and the remaining seven are initiatives from individual researchers. For some projects the

EHDN funding was just partial. Quality and number of applications have varied within different calls. Proposals have been restricted to endorsements by a Working Group. The evaluation of projects has been based mainly on the scientific merit of the proposals. Applications of funding for short/medium-term Working Group activities (or human resources) have competed with partial grants for single research projects.

Data mining projects

To date, 28 projects applying to use clinical data collected through REGISTRY have been submitted, and nine projects applied for the use of biomaterials. Time required to access data and biological materials, the electronic format into which these data are exported, the quality of data, and the lack of centrally coordinated biostatistical or methodological support have been identified as bottlenecks in this project category.

Clinical studies

Observational trials

REGISTRY

REGISTRY is a multi-centre, multi-national observational study with no experimental treatment. It aims to:

- Obtain natural history data on a wide spectrum of individuals affected by HD
- Relate clinical characteristics with genetic factors ('genetic modifiers') and data derived from the study of body fluids (blood and urine, also called 'wet biomarkers')
- Expedite identification and recruitment of participants for clinical trials
- Plan for future research studies (observational and interventional trials) aimed at better symptom control and postponing the onset or slowing the progression of HD
- Develop novel measures to track and/or predict disease onset and progression, as well as improve the existing tools.

Overall, 7,065 participants were enrolled in REGISTRY at 127 study sites from 19 countries in December 2010 [Landwehrmeyer, GB 2010]. By the end of 2010, 744 pre-manifest HD mutation carriers were participating in REGISTRY, and a number of participants at risk for HD but with unknown genetic status were enrolled. In addition, 417 control subjects agreed to take part in REGISTRY.

The total number of visits since REGISTRY started raised to over 17,500 by the end of 2010. The number of participants with more than one visit was close to 4,000 in December 2010; for more than 2,362 participants, there are at least three visits on record. This provides data for a meaningful longitudinal analysis and the calculation of trajectories reflecting individual rates of disease progression. More than 5,150 participants have donated biosamples (blood and urine) by the end of 2010. There is a steady flow of submissions at an average rate of almost 210 samples per month.

In 2010, efforts from the REGISTRY project management team have focused on preparing REGISTRY version 3 for launching, which occurred in June 2011.

TRACK-HD

TRACK-HD is a multi-national, prospective, observational biomarker study of pre-manifest and early-stage HD with no experimental treatment. It aims to develop novel assessments and to test their sensitivity for detecting very early indicators of disease onset and progression. The ultimate goal is to establish what combination of measures is the most sensitive for detecting early changes over the natural course of HD. This would lay the foundations for the development of much-needed methodology to undertake future clinical trials of disease-modifying drugs in HD. The study, which is being conducted in four sites (London, Leiden, Paris and Vancouver), enrolled 123 control subjects, 120 premanifest HD gene mutation carriers and 123 patients with early HD.

Cross-sectional analysis of baseline data was reported in 2009 [Tabrizi SJ et al 2009] and longitudinal findings from the analysis of the 12-month follow-up data were recently published [Tabrizi SJ et al 2011]. TRACK-HD has evolved from the Biomarkers Working

Group under the leadership of Sarah Tabrizi and represents a model of how working group activities can develop into a multinational clinical study with conclusive results. TRACK-HD has a well-defined scientific board, receives full funding from CHDI and has one study site outside EHDN and co-investigators from USA, Canada and Australia in addition to those in EHDN.

Interventional trials

Amarin

A placebo-controlled phase III clinical study of ethyl-EPA (Miraxion), an omega-3 fatty acid, was conducted in HD patients in Europe by EHDN and in North America by the Huntington Study Group (HSG). The study was sponsored by Amarin Neuroscience Ltd (UK). The trial, concluded in 2007, showed no statistically significant differences in the primary or secondary endpoints between patients receiving ethyl-EPA (one gram twice daily) or placebo for six months. The report of the study awaits submission for publication. A first draft of the manuscript is planned to be submitted to the study advisory board.

MermaiHD

MermailHD is a randomised, double-blind, placebo-controlled phase III clinical study in 437 patients at 32 clinical centres across Europe. It was aimed to examine the effects of pridopidine (trade name Huntexil®), a dopaminergic stabiliser, on different phenotypes of HD. Preliminary findings were made public in February 2010 by the study sponsor NeuroSearch. In parallel to MermailHD in Europe, another clinical trial of pridopidine (the HART study) was being conducted in North America by the HSG. In December 2010, NeuroSearch announced the results of a meta-analysis of pooled datasets from both studies.

Horizon

Horizon is another randomised, double-blind, placebo-controlled phase III clinical trial being conducted at 64 sites in Europe by EHDN, in North America by HSG and in Australia (PI: Karl Kieburtz, University of Rochester, USA; Co-PI: Bernhard Landwehrmeyer, University of Ulm, Germany). The study sponsors are two pharmaceutical companies:

Medivation Inc. and Pfizer Inc. EHDN assisted with several aspects of the trial management, including protocol training, translations, ERB submission, source data verification at 26 sites in seven countries throughout Europe as well as with bridging any communication gaps between the sites and the CRO.

Other clinical trials

EHDN supported the preparation/implementation of a randomised, placebo-controlled clinical trial aiming at exploring the efficacy of bupropion in improving apathy in HD patients. This study was initiated by Josef Priller and Erik van Duijn and was recently approved by the Executive Committee. It is sponsored by Charité-Universitätsmedizin Berlin, Germany, and co-sponsored by the Huntington Society of Canada.

In addition, EHDN has assisted Novartis with a short-term proof-of-concept clinical trial at six study sites in the UK and Germany exploring the anti-choreatic potential of a novel mGluR5-antagonist.

These initiatives clearly show that EHDN is in a good position to conduct large, good-quality and conclusive clinical trials. On the other hand the procedures to implement academic trials have faced several obstacles from the guarantee of full sponsoring to questions related with the role of promoter.
It is in the interest of pharmaceutical companies to test their drugs, and EHDN itself does not have a drug pipeline. EHDN has become a valuable contributor to clinical trials by providing i) HD expertise, ii) support in subjects recruitment, and iii) site management activities in 14 European languages through a team of 25 Language Coordinators based in 12 countries.

Publications

See Appendix 1

Other outputs

Development and validation of clinical rating scales.

Development of training videos and certification processes.

Conclusions

This first analysis of the research activities carried out by the different research units of EHDN, including observational and interventional clinical trials, from 2004 to 2010 has yielded the following findings:

- There are several research projects ongoing and being planned, but the expected outcomes do not always share a common thread.
- EHDN's core study REGISTRY is building a large collection of clinical data and biological samples, which will allow research projects to be conducted on an unprecedented scale.
- TRACK-HD is yielding valuable findings in the search for biomarkers of disease progression in premanifest and early-stage HD, which will pave the way for the conduct of disease-modifying clinical trials in the future.
- The current model of research within EHDN relies on the working groups' role of providing an infra-structure and facilitating communication, combined with research opportunities (both the availability of clinical and biological data and funding).
- Although these resources provide a fertile ground, results are a product of action (= research), and this action is initiated by ideas, which are the fruits of the voluntary work of EHDN's active members.
- There is a lack of interaction between the different Working Groups, particularly those with common research topics/aims.

Objectives of the Scientific Strategic Plan

Aspirational Objectives

- Cure HD
- Place EHDN as world-leader in HD research and as a clinical/research network model

Commitment Objectives

- Improve HD patients healthcare
- Produce data that will allow the design of conclusive clinical trials
- Develop a network of clinical sites capable to conduct efficiently clinical trials

Objectives for 2011-2015

During the process of development of this document, the Scientific Strategic Plan Team, in consultation with lead facilitators of the Working Groups and members of the Scientific and Bioethical Advisory Board, has established the following mid-term overall objectives to be accomplished by EHDN from 2011 to 2015:

- **Objective 1**: to improve HD patients' health outcomes
- **Objective 2**: to improve the design of good-quality clinical trials
- **Objective 3**: to expedite conclusive clinical trials
- **Objective 4**: to enhance the understanding of the progressive phenotypic spectrum of the disease
- **Objective 5**: to enhance the development of efficacious treatments (both pharmacological and non-pharmacological)
- **Objective 6**: to enhance the understanding of the disease mechanisms
- **Objective 7**: to facilitate transfer of scientific evidence to clinical practice
- **Objective 8**: to improve HD family members' health outcomes

- **Objective 9**: to increase knowledge and recognition of EHDN as an European research network.

Objectives for 2011-2013

The team and its consultants have selected four of the above mentioned objectives as short-term objectives to be accomplished between 2011 and 2013. These are:

- **Objective 2**: to improve the design of good-quality clinical trials
- **Objective 3**: to expedite conclusive clinical trials
- **Objective 4**: to enhance the understanding of the progressive phenotypic spectrum of the disease
- **Objective 9**: to increase knowledge and recognition of EHDN as an European research network.

These objectives were defined and agreed by consensus.

Strategies / initiatives to reach objectives

All strategies should be based on the objectives that were previously defined and assumed as priorities. The measures planned to achieve the objectives should be detailed and defined with explicit timelines.

The following strategies were defined to achieve the priority objectives:

1. **Improve scientific governance**
2. **Implement support facilities to improve scientific output**
3. **Improve EHDN's capability to design good-quality clinical trials**
4. **Improve EHDN's capability to conduct clinical trials**
5. **Refocus the objectives of all active groups (mainly WGs) in accordance with EHDN´s main mission**
6. **Optimise research funding**
7. **Stimulate scientific collaboration**
8. **Improve training (scientific and clinical)**
9. **Improve communication (between the EHDN groups and with the HD community) and EHDN's public recognition**
10. **Develop an innovation area**
11. **Guarantee sustainability**
12. **Monitor the plan implementation**
13. **Review the plan**

Improve scientific governance

Creation of a Scientific Planning Committee

The acknowledgment of

a) the dissociation between the current scientific potential and EHDN's output
b) the need for coordinating the interaction between WGs (and other EHDN and external research functional units)
c) the lack of scientific efficiency of the current REGISTRY steering committee format (at this stage)
d) the need to move to a higher level (and top-down) decision strategy,

suggested that an alternative model should be considered for scientific governance in the Network, as well as a need for a formal decision-making structure responsible for planning and coordinating the Network's scientific activities. The closest structures to this task are the EHDN Executive Committee (EC) and the SBAC, but both have explicitly different tasks and responsibilities. The creation of the Science Director position has already targeted this problem; however the main aspects should be outlined by a committee composed of professionals with different expertise and scientific backgrounds.

Having assumed this, it is recommended that a **Scientific Planning Committee** be created to have as its main roles:

a) planning scientific activities promoted by EHDN
b) facilitating the interaction between EHDN's different scientific functional units, namely the WGs and the PIs of all EHDN´s promoted studies.

The **Scientific Planning Committee** will be in charge of:

a) identifying the scientific needs that may be targeted by the EHDN's initiatives
b) suggesting, promoting and implementing measures to achieve the established aims keeping in mind the EHDN's mission.

The Scientific Committee will link the research strands carried out by each Working Group by providing a discussion forum with representatives from all research units, including the main investigators of ongoing research, the EC and the SBAC members. In addition, it will enhance the interaction of EHDN with external research groups, such as CHDI, The Latin America HD Network, the Huntington Study Group (HSG) as well as other networks and societies for rare or neurodegenerative disorders such as Alzheimer's and Parkinson's disease.

The Scientific Committee should work alongside the SBAC in the EHDN structure. It should report to EHDN EC and be composed by a limited number of EHDN members (5 to 7) selected by the EC with a predefined term. Its members should be well-known scientists with a global knowledge of the EHDN structure and be motivated to play a key role in furthering EHDN's scientific mission. The Scientific Planning Committee may integrate members of value from other organisations as external advisors to contribute to its goals.

Creation of a Clinical Trials Task-Force

The growth of tasks related to clinical trials, as well as EHDN's current activities and the increasing demands that these events have put on the EHDN's structure is well known (contact with the pharmaceutical industry and multiple services being offered). It is also known that no group is currently working specifically on planning and designing clinical trials. There is also a need to create internal knowledge on this topic, not only on the scientific/methodological aspects but also in all the logistic and facility requirements that guarantee the efficient planning and conduct of clinical trials.

The creation of a clinical trials task-force is proposed to improve the planning of all activities related to clinical trials (advisory boards, interaction with sponsors/promoters, selection of centres, defining EHDN services to allocate, etc.). These activities should be established in collaboration with the Scientific Planning Committee, the WGs and the other EHDN methodological support facilities.

The Clinical Trials Task-Force will be in charge of providing consultancy (or nominate experts) on the design of future clinical trials, developing the clinical study protocol, defining which centres will participate and their geographical distribution, etc. The Clinical Trials Task-Force

should work side by side with the Scientific Planning Committee and the SBAC. It should report to EHDN EC and be composed by a limited number of EHDN members (5 to 7), nominated by the EC, with a predefined term. Its members should be well-known clinicians, clinical pharmacologists or methodologists with experience in the field of clinical trials, from the research perspective to the interaction with potential sponsors. They should have a deep knowledge of the EHDN's structure as well as motivation to play an important role in this EHDN's priority mission. The Clinical Trials Task-Force may integrate members of value from other organisations to contribute to the achievement of its goal.

Creation of the Research Manager Position

It is advisable to define a full-time research manager position because of the increase and complexity of the scientific tasks conducted within the EHDN and the need to coordinate the implementation of new strategies. The research manager's main mission should be to contribute to the development of HD research in line with the EHDN's Scientific Plan and implementation of the assigned projects and tasks.

The research manager should report to the Science Director and may have these main tasks:

a. Contribute to the scientific governance of EHDN towards project management organisation for clinical research
b. Identify and lead assigned projects from the Scientific Planning Committee and Clinical Trials Task-Force and ongoing projects to successful planning, execution and reporting
c. Facilitate multiple group collaboration on projects where EHDN has the leading role
d. Scientific coordination between task-force groups within a centrally prioritised project, project planning
e. Use of REGISTRY data and other data available from the EHDN's clinical research on HD's trial methodology for conducting informative clinical studies
f. Organise expert and potential partner meetings for specific scientific issues

g. Be an ambassador of the EHDN and its potential as a clinical research centre par excellence for HD
h. Contribute to the development of a portfolio and optimising fellowships and grand application
i. Guide medical writer on project preparation/calls
j. Establish contacts and possible project fellowships with other organisations

Reorganise EHDN staff support

An EHDN staff member should be assigned to be the project manager of each initiative in order to optimise the conduction and efficient managing of the different committees and scientific projects. Therefore, all EHDN promoted projects should have a designated member of the staff allocated as research coordinator.

Short-term initiatives:

i. **Creation, definition, composition and procedures of the Scientific Planning Committee.**
ii. **Creation, definition, composition and procedures of the Clinical Trials Task-Force.**
iii. **Definition of the research manager position description for the EHDN.**
iv. **Redefinition of the EHDN LANCOS' tasks and other staff members allocated to specific projects according to their background and motivations.**

Implement support facilities to improve scientific output

The main objective of this step is to maximise the scientific output of the EHDN, its research centres or single investigators. The scientific output is closely associated with the dissemination of research results obtained by studies conducted within the EHDN or other projects fostered by the EHDN. By making it easier to publish data or results, we are making sure that we practise the principle of scientific data sharing, therefore contributing to turning EHDN into the lead research network for HD.
By placing EHDN as a world-leader and clinical/research network model for HD research, it guarantees:

a) Drawing of attention to the high-quality research projects being carried out
b) Capability to recruit and motivate new active members and centres

Support facilities have to be created to help the EHDN's members to combine their clinical tasks and other research duties with the conduct and publication of the EHDN's promoted or endorsed project results. The implementation of the following facilities is recommended:

Biostatistics support facility

The objective of a statistical support facility is to provide research studies biostatistics support for planning, conducting, evaluating, and reporting. This support should be available to EHDN's active members. The services provided by such a facility would include statistical support services from the development stage to the analysis and dissemination of research results, including designing statistical analyses, study design, sample size estimation, data analysis, and reporting of statistical results. It may also assist with the development or review of the methodological aspects of protocols and manuscript preparation.

The Network has recognised that biostatistics support is a key element to facilitate the conduct of research within EHDN. Procedures are being created to offer this service to the EHDN community. The priorities were defined as a conclusion of the statistical plans for the REGISTRY sub-studies (planned to move to the ENROLL study) and the conclusion of WG's ongoing statistical analysis of REGISTRY data. The definition of statistical plans for the

evaluation of data quality and the update on the prospective data of REGISTRY is also to be included.

Clinical methodology support facility

The overview of the past and current EHDN's activities identified the domains of epidemiology and clinical outcomes as weak areas of research. The need to prioritise the aspects related to the development of patient-centred outcomes and validated clinical scales for specific clinical problems / disease stages and qualified progression biomarkers means that we should involve professionals from the fields of epidemiology and clinical outcomes in the current research activities. It is recommended that a clinical outcomes working group be created.

Medical writer support facility

There is a dissociation between concluded EHDN studies and the corresponding manuscripts being submitted for publication because of the limited time researchers and clinicians have to write and edit the manuscripts. The access, priorities and relevance for the HD community of the dissemination of those results should go hand in hand with the Network's main mission and defined objectives. This facility will assist professionals in the creation of manuscripts for peer-reviewed journals and other types of scientific documents or publications as required. This service is already available in the EHDN structure but could be optimised and facilitated and more focused on the scientific outputs (manuscripts).

Designation of a study coordinator from the EHDN staff for every project

As mentioned above in the section about scientific governance, it is recommended that a research coordinator is designated from the EHDN staff for every project. The research coordinator will manage research and report to the EHDN research manager and Science Director.

Transitory plan to conclude ongoing studies

It is suggested that a transitory plan be implemented in order to identify projects using REGISTRY data or EHDN-endorsed projects that are overdue or that have been concluded but not published. The reasons for the delay should be identified for every study and a specific plan should be elaborated to facilitate its conclusion. The reasons for lack of conclusion of any research study must be explicitly stated on the EHDN web portal and the study should be removed from the list of ongoing studies. It should also be stressed that for new projects publication is expected or reasons given and the above action will happen

EHDN scientific fellowship

The recognition of gaps in the EHDN outputs related to the accomplishment of its mission and now defined priority objectives suggest the discussion of possible research support models that may guarantee the needed results. This conclusion recommends the implementation and support of EHDN scientific fellowships in order to approach scientific issues defined by the Scientific Planning Committee. These fellowships should have a 1 to 3-year time period and their applicants should be carefully selected according to the key points defined by the Scientific Planning Committee and in line with the EHDN mission.

Short-term initiatives:

i. **Creation and definition of access rules to the biostatistical support facility;**
ii. **Creation and definition of access rules to the medical writers' support facility;**
iii. **Plan for a transitional period (6 months) to facilitate the conclusion and presentation of results from delayed studies, EHDN-endorsed studies or projects aimed at the analysis of REGISTRY data;**
iv. **Promote the creation of a clinical outcomes working group/task-force;**
v. **Regulation for defining and implementing the EHDN scientific fellowships.**

Improve EHDN capability to design good-quality clinical trials

To maximise EHDN's capability to respond efficiently to the incremental list of scientific and logistical tasks related to clinical trials, it is advised that we :

a) Create a Clinical Trials Task-Force.
b) Implement mechanisms to conduct all scientifically relevant analysis from REGISTRY and other EHDN-related studies, thus increasing knowledge on how to design clinical trials
c) Support the development, validation and qualification of progression markers
    i. Facilitate the optimisation of the analysis of the most promising progression biomarkers
        1. e.g. Imaging repository
            a. definition of recommended imaging protocol
            b. integration into existing imaging repositories

Short-term initiatives:

i. **Create Clinical Trials Task-Force.**
ii. **Implement the EHDN CLINICAL TRIALS PROJECT (see section on Improve EHDN capabilities to conduct clinical trials).**
iii. **Define a list of potential missing data and analysis which can be extracted from REGISTRY and other accessible studies (e.g. COHORT).**
iv. **Define mechanisms that generate dynamic outputs based on the EHDN accessible data.**

Improve EHDN capabilities to conduct clinical trials

The capability of EHDN sites to participate efficiently in the conduction of clinical trials represents a priority for the achievement of EHDN's objectives. This capability is related to two main factors: capacity to recruit adequate subjects in a reasonable time frame and the overall quality of the data produced. The steps to achieve this objective may be called: **EHDN clinical trials project**. This project's main objective should be to define the most relevant factors from the centre's perspective and from the participants' perspective to guarantee a successful recruitment rate. The second element should be related to the definition of the sites' minimal requirements to guarantee good quality data.

Short-term initiatives:

i. **Define the EHDN clinical trials project's programme**
ii. **Support research projects with the objective to identify key factors for good clinical trial site performance**
iii. **Create an EHDN clinical trials portfolio (including information on sites)**
iv. **Define the minimal requirements for an EHDN clinical trial site**
v. **Define a programme to optimise patient recruitment**
vi. **Define and allocate EHDN clinical trial projects staff**
vii. **Create a clinical trial EHDN services' manual**
viii. **Implement measures to facilitate the sustainability of good-quality HD clinical trial centres**

Refocus working group objectives

Following the webinars on January 31st and February 3rd 2011 and Strategic Plan Meeting that took place in London in March 2011, all leaders of Working Groups were asked to establish commitment goals for the next two and five years, for which the following information was requested:

- commitment goals
- currently faced challenges, bottlenecks and deficits
- resources (including human resources, tools, technologies, infrastructure, and financial resources) required to overcome the limitations
- timeline to achieve the goals

Through this process key data and comments were collected to define the proposals incorporated in the other sections of this document. This request was also a way of sharing the need to redefine the ongoing and future projects based on the agreed priority objectives and Strategic Plan.

Short-term initiatives:

i. **Request to each WG lead facilitator to redefine short- and long-term objectives and initiatives according to the new Strategic Plan.**

Optimise research funding

The functional structure of EHDN is mainly based on the voluntary contribution of single researchers and clinical centres. This makes it crucially important to define mechanisms to support relevant research. The current mechanisms for funding research within EHDN include the direct support of WGs' annual meetings, the support to the seed funds grants and the direct funding of specific projects proposed by the WGs or single centres. The facilitated use of EHDN structures or facilities also result in other type of direct and indirect funding.

In the overview of the Network's research activities, a need to stimulate the interdisciplinary collaborative research was found as well as to clarify the exact type of support WGs were receiving, as this was sometimes masked under a seed fund application format. Based on this evaluation, it is suggested to continue seed fund applications. However, it should not be mandatory to have the endorsement from the WGs but favour collaborative projects instead. The spirit behind the seed funds applications should remain the facilitation of the conduction of exploratory studies or innovative ideas.

On the other hand, it is suggested a mechanism be created that will support the research activities of the WGs directly. These funds should allow the implementation of projects based on the Network's main objectives, be restricted to WGs, favour objectives close to the EHDN's mission and collaborative WG projects.

Short-term initiatives:

i. **Change seed fund regulations in accordance with the new type of grant applications.**
ii. **Define a distinction between seed research (a catalyst to progress by encouraging innovation in new areas of research relevant to EHDN) and enabling research (will advance research that would not move forward without internal or external support).**
iii. **Identify new revenue streams to support the EHDN activities and other initiatives that address the EHDN's objectives.**

Stimulate scientific partnerships

The current EHDN partnership politics reflect the natural relationship with CHDI, mainly because CHDI is its main sponsor and because of its common working areas. Collaboration with the HSG occurs mainly regarding the conduct of clinical trials or specific projects. There is no formal collaboration with clinical centre networks or other degenerative disease networks, especially in terms of clinical collaboration or resulting from interest in the same methodological aspects. Collaboration with the pharmaceutical industry is moving from just facilitating the conduct of clinical trials to a more active role in the early stages of drug development and planning of clinical development.

Short-term initiatives:

i. **Stimulate interactions with other neurodegenerative research networks, particularly in the field of rare diseases, Alzheimer's disease and Parkinson's disease.**
ii. **Invite EHDN's external experts to actively participate in the EHDN committees as external advisors.**
iii. **Organise a scientific forum that focuses on clinical trial methodology to present the EHDN's capabilities and services to all pharmaceutical (potential partners) companies interested in HD.**
iv. **Develop the concept of 'EHDN Ambassador'. Assign a different and specific ambassador role to the EC members and other key EHDN members.**

Improve scientific and clinical training

The regular activities of EHDN and the analysis of the data of REGISTRY have documented quality problems that may benefit from an investment in the clinical and methodological training of all the partners contributing to the clinical evaluations, monitoring and data management. There have been already important EHDN training activities related to the certification of the UHDRS motor raters and other scales; at the last EHDN plenary meeting in 2010, teaching courses were implemented for the participants. It is suggested that clinical training fellowships and support should be implemented in order to optimise scientific output.

Short-term initiatives:

i. **Implement methodological training about aspects relevant to the quality of data collected in clinical studies.**
ii. **Develop and deliver innovative educational models that reflect the needs of EHDN projects and HD healthcare professionals.**
iii. **Develop EHDN clinical fellowships.**
iv. **Develop teaching courses about the following topics:**
    a. **clinical HD for basic scientists**
    b. **preclinical research methodology for clinicians and other healthcare professionals**
    c. **clinical trial methodology**
    d. **application of HD rating scales**

Improve communication and EHDN's public recognition

A communication plan should be developed for recruiting subjects for clinical studies. Particular attention should be given to factors that may interfere with the motivation for taking part in clinical trials. Among other measures, the representation of the EHDN at international meetings as well as the elaboration of a portfolio should be included in a publicity material to ensure that EHDN plays a key role as a model for other clinical research networks investigating orphan diseases in Europe.

Short-term initiatives:

a. **Develop a *communication plan* focused on recruiting subjects for clinical studies**
b. **Develop an EHDN introduction video**
c. **Encourage EHDN members to promote the Network when participating in other meetings (e.g. EHDN slides with logo, information about the EHDN website, video)**
d. **Enhance internal communication between WGs, Committees, Task Forces and EC (consider new forms of communication (e.g. webinars))**
e. **Clarify and communicate the internal organisational structure to members**
f. **Brand EHDN as an international organisation involved in HD research and care**
g. **Identify strategies to enhance website visibility (e.g., search engines optimisation)**
h. **Increase EHDN awareness among patient groups and healthcare professionals**
i. **Improve EHDN's public recognition**

Development of an innovation area

It is important that research networks, although mainly focused on their topics, define a particular scientific area as a key element of pioneering and innovation. With this in mind, we consider relevant to develop a research area called “Translational Research” that can be a groundbreaking topic suitable to a pathology such as HD and ready to be exploited through the structure and type of data accessible through EHDN. The fact that HD constitutes a rare disease for which there is a highly specific marker for diagnosis and data available from several prospective cohorts constitutes in itself an excellent resource to conduct translational research. All discussions about the best design to condutct clinical trials, assessment of the interference of the intervention on disease progression in prodromal stages make this concept relevant.

A number of new technologies that can aid bioscience and clinical research are emerging. They may enable analysis of large datasets, such as those generated in genome-wide association studies, transcriptomics, metabolomics, proteomics and other studies using high-throughput techniques, disease modelling and ultimately a better understanding of the molecular pathogenesis of diseases. This innovative area includes Networks and Systems Biology, Bioinformatics and Biomathematics as well as other computational sciences. The Biological Modifiers WG has already been exploring these approaches.

Short-term initiatives:

i. **Definition of translational research as the area of innovation within EHDN**

Implement mechanisms to guarantee sustainability

Currently, the main structure of EHDN is almost entirely funded by CHDI. Despite this privileged situation, the leaders of the EHDN should plan the sustainability of the Network by anticipating any changes in the model of cooperation and funding that currently exists. In this sense, there should be planned alternative financing sources outside the Network. With this in mind, mechanisms should be created for application to all national or international funding sources for research monies that fit the HD concept (neurodegenerative diseases, orphan diseases, etc.).

The recommendations are:

1. Individually or globally, the Network should apply for all grants that are in consonance with and support the overall objectives of the Network;
2. This objective should be implemented through the following steps:

a. Development of a dynamic dossier (EHDN portfolio) constituting an asset for submission to local calls with available information for all members;

b. Implementation of mechanisms to identify and alert to open grant calls for European, international or national grants;

c. Creation of internal mechanisms that will facilitate the preparation of documents for the application to these grants;

d. Identify companies or individuals that coordinate the preparation of projects to apply as candidates.

EHDN should support all applications to grants or other projects at national or European level. A dynamic register of calls should be created to alert mechanism to candidates.

Short commitments:

i. **Implement mechanisms to identify calls for HD research.**
ii. **Develop an updated EHDN portfolio for call applications at different forums.**
iii. **Identify science management providers.**

Monitoring of the plan implementation

Periodic monitoring mechanisms should be used when implementing the Strategic Plan. This should apply to the overall plan and be extended to the implementation of all projects that require EHDN funds, any participation of direct or indirect EHDN resouces, members on behalf of EHDN or EHDN facilities. All projects must define objectives, expected deliveries and timelines for the sequential actions.

It is recomended that appropriate outcome measures be established for each activity to assess the success of each programme.

Review of the Plan

Two years after the implementation of the Strategic Plan, an interim audit should be undertaken for the Network. A formal audit should be undertaken after five years, preferably conducted by external auditors, coinciding with the completion of this Plan, and should be followed by the preparation of a new plan for the next time period.

Appendix 1

Publications authored by EHDN

1. Landwehrmeyer GB, Dubois B, de Yébenes JG, Kremer B, Gaus W, Kraus PH, Przuntek H, Dib M, Doble A, Fischer W, Ludolph AC, and the European Huntington's Disease Initiative Study Group. Riluzole in Huntington's disease: a 3-year, randomized controlled study. *Ann. Neurol.* 2007;62:262-272
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Publications resulting from Working Group activities

Biomarker WG

1. Tabrizi SJ, Scahill RI, Durr A, Roos RA, Leavitt BR, Jones R, Landwehrmeyer GB, Fox NC, Johnson H, Hicks SL, Kennard C, Craufurd D, Frost C, Langbehn DR, Reilmann R, Stout JC; TRACK-HD Investigators. Biological and clinical changes in premanifest and early stage Huntington's disease in the TRACK-HD study: the 12-month longitudinal analysis. *Lancet Neurol.* 2011 Jan;10(1):31-42.
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Imaging WG

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Standard of Care WG

1. A Standard of Care for Huntington's Disease: Who, What and Why
2. A Guideline for Oral Health Care of Adults with Huntington's disease
3. Nutritional Management of Individuals with Huntington's Disease: Nutritional Guidelines
4. Speech, Language and Communication in Huntington's disease
5. The Swallowing Disorder in Huntington's Disease: A Guideline Document for Speech and Language Therapists working with Huntington's Disease patients
6. A Guideline for Occupational Therapy in Huntington's disease
7. Development of physiotherapy guidance and treatment-based classifications for people with Huntington's disease (contributed by the Physiotherapy Working Group).

Quality of Life WG

1. Hocaoglu MB, Gaffan EA, Ho AK. The Huntington's Disease health-related Quality of Life questionnaire (HDQoL): A disease-specific measure of health-related quality of life. *Clinical Genetics* 81(2), 2012,117-122
2. Hocaoglu MB, Gaffan EA, Ho AK. Health-related quality of life in Huntington's disease patients: a comparison of proxy assessment and patient self-rating using the disease-specific Huntington's disease health-related quality of life questionnaire (HDQoL). *J Neurol* 2012 Mar 6. [Epub ahead of print]

Appendix 2

Projects approved by the Executive Committee after endorsement by the Scientific and Bioethical Advisory Board

Author	Title of project
Aguirre Escobal, Ana	Search for candidate genes implicated in Huntington's disease (HD) age of onset (AOO)
Barker, Roger	Tau haplotype and its relationship to age of onset and disease progression in Huntington's disease
Björkqvist, Maria	Muscle pathology in HD as a source for biomarkers?
Busse, Monica	Are there specific lifestyle factors that could be associated with the HD clinical characteristics and progression thereof: a retrospective data mining study?
Busse, Monica	Reliability and minimal detectable change of measures of participation, functional activities and impairments in individuals with Huntington's disease
Coelho, Miguel	Late stage HD: phenotype and current management
Crooks, Jennifer	A data mining project investigating psychosis in Huntington's Disease
EHDN	Defining the phenotype of Huntington's disease in Europe: The European Huntington's disease Network REGISTRY Study
Frich, Jan C.	Memantine treatment in the REGISTRY cohort
Frost, Chris	Using REGISTRY data to inform choice of outcome measures and optimal design of future clinical trials in Huntington's Disease
García de Yébenes, Justo	Impact of education on age at onset and progression of HD

Giorgini, Flavio	Copy number variation of potential genetic modifiers of Huntington's Disease
Gruber, Beata	The studies on the biochemical markers characterizing Huntington´s disease –determination of the profile of common amino acids in the serum of patients in different stages of Huntington´s disease
Gusella, James	Genome Wide Association Scan to Identify Modifiers of HD Onset
Hoo, Aileen	Towards an improved Functional Rating Scale for Pre-Huntington's Disease
Kassubek, Jan	Parameter optimisation for diffusion tensor imaging in Huntington's Disease
Keylock, Jenny	The familiality of psychiatric symptoms in Huntington´s disease
Keylock, Jenny	The use of depression rating scales in patients with HD
Krzyszton-Rusjan, Jolanta	Molecular mechanisms of BCAA and energy metabolism study in peripheral blood mononuclear cells of Huntington's disease patients
Kwak, Seung	Genome-Wide Genotyping of EHDN Samples
Lange, Herwig	Understanding prescribing habits of existing potential neuroprotective substances in HD
Mestre, Tiago	Prescription habits in Huntington's disease
Metzger, Silke	Analysis of potential modifier genes involved in intracellular trafficking and mitochondrial function
Myers, Richard	An assessment of CAG repeat length and age at onset on rate of disease progression in Huntington´s disease
Neri, Christian	Search for genetic modifiers in HD: exploring the Foxo network
Orth, Michael	The accuracy of the estimation of age at onset of motor signs in HD

Orth, Michael	Data quality in REGISTRY: completeness, plausibility and the effect of monitoring
Quarrell, Oliver	Measuring outcomes in Huntington's disease
Quarrell, Oliver	Survey of Pharmaceutical interventions in JHD
Rickards, Hugh	Depression in Huntington's disease, its treatment and associations
Saft, Carsten	Sex-specific differences in AO
Tabrizi, Sarah	Identification of genetic modifiers of age of onset in HD. Candidate gene study of CR1, CLU, PICAM, PRNP and APOE
Tedroff, Joakim	Investigation of Time Course and Functional Impact of Voluntary Motor Function Impairment in Huntington's Disease
Wanker, Erich	Hunt for Huntington modifiers with systems biology approaches
Weydt, Patrick	PGC-1a as a potential modifier gene of age of onset of HD
Zielonka, Daniel	Influence of gender on progression of HD

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