March 2022 · Issue 45

EHDN *News*

EUROPEAN **HUNTINGTON'S DISEASE** NETWORK

Photo: Hans Braxmeier

Welcoming 2022...

Catherine Deeprose

Following the challenges of the past year, we move into 2022 with renewed purpose and optimisim – and we have much to be positive about in the HD Community. Our 45th edition of EHDN *News* opens with a discussion on the exciting update from Roche on their tominersen development programme and future plans for the drug. We also hear from current EHDN Scientific and Bioethics Advisory Committee chair, Kathrin Reetz, about the responsibilities and challenges associated with committee membership as we approach the important run-up to elections in September this year. Jane Simpson and Maria Dale give us an insight into the Psychological Interventions and Approaches Working Group, and we hear first hand about the experiences of delegates at the recent MDS-ES and EHDN Joint Online Course Series. Finally, it is with the greatest pleasure that we meet Charles Sabine, OBE, to hear about his vital work in breaking down boundaries in HD and being 'hidden no more'.

OUR PHOTO EXPERIMENT CONTINUES – SHARE YOUR OWN! SEE PAGE 14

CONTENT — Click the Page

www.ehdn.org

Subscribe to EHDN *News*:
Please go to the URL below and fill out the online form:
http://www.ehdn.org/news-events/
Please send us your comments, suggestions and overall feedback:
newsletter@euro-hd.net

Imprint:
Editorial Board of EHDN *News*:
Catherine Deeprose, Editor
Gabriele Stautner Artifox Communication Design (Ulm, Germany).

What's Next for the Tominersen Development Programme?

Catherine Deeprose, Tim McLean, Anne Rosser, Patrick Weydt

On 20 January, the EHDN hosted an online presentation by Roche on their tominersen development programme. Anne Rosser opened the eagerly anticipated and well-attended event with a warm welcome and introduction to our speakers from Roche, Peter McColgan and Lauren Boak.

Photo: EHDN

Lauren Boak

Lauren began by recapping on the Roche/Ionis HD partnership which began in 2013, and how the Phase I/IIa study of tominersen had shown a well-tolerated, favourable safety profile for up to 120 mg tominersen in early manifest HD, as well as evidence for a lowering of mutant huntingtin. These data, as well as the underlying scientific rationale, led to the expedited progression of tominersen to a Phase III trial in 2019 – what we all know as GENERATION-HD1.

Following disruptions arising from a restart in 2019 and then, of course, COVID-19 from 2020 to 2021, GENERATION-HD1 dosing was unexpectedly stopped mid-trial in March 2021. This was the result of recommendations from the independent data monitoring committee (iDMC) based on the overall risk/benefit of tominersen. The iDMC have since advised that their assessment of the off-treatment data gathered for up to 6 months indicated there were no long-term effects in any participants and no further formal safety follow-up for the trial was required.

Since March 2021, the Roche team has been busy conducting planned and exploratory analyses, and a large proportion of study participants in both GENERATION-HD1 and GEN-EXTEND have continued to be followed for safety and clinical outcomes. Both studies will complete in March/April 2022 and participants in GENERATION-HD1 will be unblinded as to whether they received tominersen or placebo by mid-June 2022. There will, of course, be keen interest in the longer-term safety signals in the participants that received tominersen.

Lauren finished by recapping the observations communicated following the discontinuation of dosing last March. These were that tominersen 120 mg given once every 8 weeks had unfavourable clinical outcomes at the group level and the less frequent dose regimen – tominersen 120 mg given once every 16 weeks – was not different from placebo.

Photo: EHDN

Peter McColgan

Peter then talked us through the further analyses that Roche have performed on the GENERATION-HD1 data sets. The point of this further scrutinisation of the data was to understand whether any subgroups had benefitted from the treatment and whether any progress could be made in understanding the reasons for the failure of tominersen to show benefit. It's important to recognise that further analyses of this kind, performed in the face of the trial not having shown a statistically significant effect in the measures it was designed to test, are exploratory and must be viewed with caution.

Part of this further analysis involved dividing the trial participants into groups of younger versus older participants (aged below or above 48 years), and then further subdividing them according to disease burden [as defined by the CAP (CAG Age Product) score which is used to estimate the stage of HD]. This produced four subgroups: low age/low CAP, low age/high CAP, high age/low CAP, and high age/high CAP. One group – the low age/low CAP group, exposed to the lower dosing regimen (120 mg every 16 weeks)

> *'It's important to recognise that further analyses of this kind, performed in the face of the trial not having shown a statistically significant effect in the measures it was designed to test, are exploratory and must be viewed with caution.'*

– showed favourable clinical signals across multiple Unified Huntington's Disease Rating Scale subscales, most clearly at week 69, with the suggestion that some biomarkers might be moving in a similar direction.

We should reiterate that the study wasn't designed or powered to test these exploratory post hoc analyses in such small groups of participants, and so, these results cannot be taken as proof of an effect. Nonetheless, they do provide some confidence and encouragement that further exploration of tominersen is justified. Looking forward, Peter concluded that these findings suggest that a low dose of tominersen might benefit younger adult participants with a lower disease burden.

The path forward for the tominersen development programme will be a new Phase II dosing study in this specific group of participants. This is currently at the early stage of planning and Roche will share the specific details, including study design and dosing regimen, later in the year.

Photo: EHDN

Patrick Weydt

Following the presentation of these important developments, Patrick Weydt opened the floor to questions from the audience,

Photo: EHDN

Ed Wild

which were addressed by Peter and Lauren. This was followed by a lively panel discussion, moderated by Anne and Patrick, which benefitted from further insights from Holly Kordasiewicz (Ionis Pharmaceuticals, Inc.), Bernhard G. Landwehrmeyer (University Hospital Ulm), Bart van de Warrenburg (Radboud University), Ed Wild (University College London) and Michaela Winkelmann (HD Association Germany).

> *'The path forward for the tominersen development programme will be a new Phase II dosing study in this specific group of participants… Roche will share the specific details, including study design and dosing regimen, later in the year.'*

• • •

Get in touch with the Think Tank!

The EHDN's HD Science Think Tank brings together EHDN members and staff who are closely involved in supporting scientific research – including members of the Executive Committee, Central Coordination and the working groups – and it engages with the HD research community in three ways:

- Researchers may contact the Think Tank for help in identifying potential collaborators or funding opportunities, or to discuss scientific ideas
- The Think Tank welcomes suggestions of research topics, and has provided a contact form on its website via which these can be submitted
- The Think Tank may occasionally propose specific research topics that could be addressed by a dedicated task force working for a defined period of time

Photo provided by Kristina Bečanović

For more information about the Think Tank, please contact Kristina Bečanović: kristina.becanovic@euro-hd.net


Photo: Kathrin Reetz

The Scientific and Bioethics Advisory Committee – Our Responsibilities and Challenges

Kathrin Reetz (current committee chair), Ahmad Aziz, Christine Capper-Loup, Michael Orth

Responsibilities

The EHDN has a Scientific and Bioethics Advisory Committee (SBAC) that advises the Executive Committee (EC) on scientific and bioethical matters in its drive to facilitate HD research across Europe. For instance, the SBAC reviews applications for access to EHDN resources including data and biomaterials, applications for EHDN endorsement of protocols for clinical and non-clinical trials as well as other studies, applications for seed fund projects, and in addition, responds to other scientific and bioethical questions that members may raise.

Members

The SBAC consists of twelve members elected by the EHDN membership, including a chair and co-chair and three non-elected members. The SBAC members have diverse professional backgrounds ranging from neurology, epidemiology, psychiatry and neuropsychology to molecular biology and genetics (more details on the current elected members can be found here). The SBAC is supported by two co-opted members (Peter Holmans for statistical genetics and Heidi Bentzen for bioethical advice) and a patient representative (Dina de Sousa). There are two EHDN *ex officio* members, Christine Capper-Loup (EHDN Scientific Project Manager) and Michael Orth (EHDN Science Director and Professor for Neurology), both at the NeuroZentrum Siloah in Bern, Switzerland.

Our Challenges

It has now been almost 30 years since the mutation causing HD was first described. Despite encouraging progress, however, the treatment of HD remains directed towards its symptoms rather than its cause.

> *'Science develops ever more sophisticated tools to dissect the many phenotypes of HD, ranging from novel ways of imaging the brain to harnessing computer power in crunching huge data sets from thousands of people.'*

Science develops ever more sophisticated tools to dissect the many phenotypes of HD, ranging from novel ways of imaging the brain to harnessing computer power in crunching huge data sets from thousands of people. These breath-taking new technologies have enormous potential for eventually finding new treatments. However, it also means that any research that uses them needs to be reviewed by people who have a good understanding of all they encompass, including the ethical aspects.

HD is a neurodegenerative disorder characterised by a triad of signs and symptoms, including motor, cognitive and behavioural disturbances. Although HD is a monogenetic disorder, its age of onset and other clinical manifestations can be highly heterogeneous. This clinical diversity is mirrored by heterogeneity at the molecular level, where recent insights gained from both genetic association studies and *in vitro* experiments indicate the involvement of several pathogenic pathways, which often act in concert with and are modulated by the mutation size. This clinical and molecular heterogeneity is, in turn, reflected in the diverse array of (para)clinical and basic science studies – each using a plethora of various methods and approaches – aiming to understand different aspects of this complex disease. Therefore, for a judicious and fair assessment of the scientific merits and potential impact of each clinical or basic science research proposal or data application, the SBAC draws upon the collective expertise of different clinical, paramedical and basic scientists.

The fast pace of recent analytical and technological advances has boosted the development of a diverse array of promising therapeutic options. Nevertheless, these methodological advances also require specific knowledge and expertise, not only from the applicants but also the individuals who are tasked with judging the unique merits of each application seeking to leverage these cutting-edge approaches. This implies the need for in-depth knowledge of a broad range of topics across highly diverse research and clinical fields.

In fact, the array of necessary expertise at the SBAC is probably broader than most of us might immediately think: it requires in-depth knowledge of (epi)

genetic and molecular and pathogenic mechanisms, epidemiology, sophisticated statistical models, machine learning and artificial intelligence, biomarker research, digital real-world data, data protection and safety issues, multi-modal imaging, brain stimulation (including invasive deep-brain stimulation), and clinical trial design, as well as of disease-modifying approaches (e.g., neurotransmitter-replacement, excitotoxicity, mitochondrial-function and oxidative stress, modulation of neuroinflammation and RNA-approaches). Thus, to adequately fulfil its responsibilities, the SBAC must meet these highly diverse and interdisciplinary requirements, not only at the scientific level but also at the ethical level – and always in the interest of HD patients and their families.

Key Dates

Open nomination of committee positions: February–April 2022

Information presented on nominees: May–July 2022

Open elections: July–September 2022

Voting results: Announced at the EHDN Plenary Meeting in September 2022

> *'SBAC members will be appointed based on their specific expertise, ensuring representation across the full spectrum of clinical and basic sciences disciplines.'*

To broaden the scientific knowledge base of the SBAC, the process of selecting its members will be adapted. First, SBAC members will be appointed based on their specific expertise, ensuring representation across the full spectrum of clinical and basic sciences disciplines. Second, for applications for which a proper and fair judgement is not possible based on the (collective) expertise at the SBAC's disposal, external experts will be approached as additional reviewers. We think that these adaptations are necessary to face the challenges posed by the highly dynamic research landscape and, at the same time, improve the quality and impact of future HD research facilitated by the EHDN.

• • •

Working Group Focus: Psychological Interventions and Approaches

Jane Simpson (Lancaster University, UK) and Maria Dale (Leicestershire Partnership NHS Trust, UK)

The Psychological Interventions and Approaches Working Group seeks to promote the value of psychologically informed interventions and approaches to improving the lives of people affected by HD.

While a range of approaches are crucial in trying to improve the lives of people affected by HD and are reflected in the different foci of the working groups within the EHDN, the value of psychology has perhaps only more recently been acknowledged. For example, both the number of clinical psychologists working in services and the number of research studies focused on psychology are relatively small. Tellingly, a recent review of psychological interventions to improve psychological functioning in HD carried out by members of the working group identified only nine published papers, and most of these were not of high scientific quality.

The group's aims are to:

- Carry out more research to investigate the potential for psychological interventions to improve lives. A recent grant from the Gossweiler Foundation to members of the group will, for example, assess guided self-help for anxiety.
- Promote the potential for psychological perspectives to improve lives. A recent manifesto from members of the group set out principles to inform psychological care.
- Work with national charities to offer seminars on psychological care, how to access services, and what psychology means. For example, Jane and Maria, leaders of the group, recently offered a series of seminars to the England and Wales Huntington's Disease Association on different forms of psychological therapy and what they can offer.

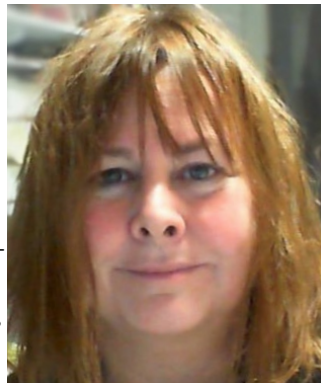


Photo: Jane Simpson

Jane Simpson

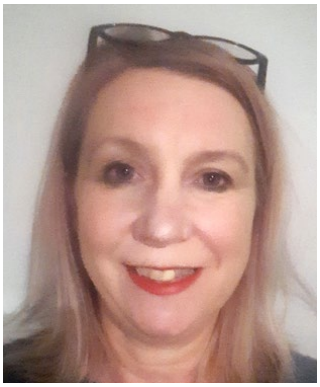


Photo: Maria Dale

Maria Dale

> *'...we really want to build on the work we and others have done in this area and continue to lobby for better psychological care for all affected by HD. Please get in touch if you are working or researching in a psychological way so we can grow this network of academics and practitioners.'*

- Look at concepts often used in HD from a psychological perspective. A recent paper looked at the concept of irritability and critiqued how the concept has been used.
- Support colleagues with information about psychological approaches and provide networking and information exchange opportunities. *NB: The next meeting of the group will be in April and current and new members are very welcome to join.*
- Carry out research exploring the lived experiences of people affected by HD, so we can root our research in the issues affecting lives on a daily basis. A recent paper looked at the experiences of pre-manifest individuals in the UK.

Areas for future focus will be to map how mental health care is provided, hopefully across Europe, so that future grants or applications can be grounded in these data to conduct further research on psychological interventions and lived experiences.

Maria explains, 'the EHDN Psychological Interventions and Approaches Working Group has enabled me to meet academics and clinicians who are similarly motivated to help improve the evidence-base for psychological approaches for people with HD. We know that currently, it is often difficult for families to find specialist HD psychological support and our ambition is, through the collaborative work of the EHDN, to change this situation and for families affected by HD to receive high-quality psychological care. We welcome new members who wish to help develop our work further.'

Jane is also keen to emphasise the opportunities for involvement, adding 'I have really valued the opportunities facilitated by the EHDN to grow interest and research in this area. Maria and I met via the EHDN and we have since met many other colleagues across the world interested and committed to improving psychological care. As we move forward, hopefully out of the difficult times created by the pandemic, we really want to build on the work we and others have done in this area and continue to lobby for better psychological care for all affected by HD. Please get in touch if you are working or researching in a psychological way so we can grow this network of academics and practitioners.'

HUNTINGTON'S DISEASE YOUTH ORGANIZATION

Huntington's Disease Youth Organization (HYDO)

HDYO's JOIN-HD: Juvenile onset HD Global Registry is now enrolling!

Jenna Heilman, HDYO Executive Director

This registry collects experiences from both young people who have JoHD and their caregivers. This will allow us to advocate for improvements to care, research and awareness. We hope JOIN-HD will be a platform that will encourage other scientists and clinicians to carry out much-needed research into this devastating disease. Find out more at HDYO.org or email registry@hdyo.org.

Breaking Down Barriers: Participating in Research
Click **here** for a video about two young people taking part in Enroll-HD.

MDS-ES and EHDN Joint Online Course Series

The MDS-ES and EHDN worked closely together to provide the Joint Online Course Series: Huntington's Disease for healthcare professionals across three Friday sessions in October 2021. Each of the three sessions was attended by about 100 participants and many more accessed the recorded lectures later.

Photo: Abdoulaye Bocoum

Abdoulaye Bocoum

Abdoulaye Bocoum, Neurologist in Training, University of Science, Technique and Technologies of Bamako in Mali, shared his experiences.

As an African early-career researcher, I am particularly interested in movement disorders, especially HD. In my country (Mali), there are no movement disorder specialists and there are no courses on movement disorders in the neurological training curriculum. For these reasons, the EHDN/MDS course provided a valuable and unique way for us to be trained in this field.

All the aspects covered over the duration of the course were relevant to me, and given the current context of lack of resources in my country, I would very much welcome the opportunity to attend future courses such as this one.

Of particular interest to me was the coverage of genetic counselling. In Mali, the reproduction rates are very high – around 6.5 children per female – and men are allowed to marry up to four wives. Most of our HD patients have already had many children, and announcing the HD diagnosis to these patients requires knowledge of genetic counselling. The materials presented in this section were very helpful for me because I obtained new skills that will benefit my patients. Currently, the responsibility for genetic counselling is not clearly defined in Mali. It could be the responsibility of a neurologist or a psychiatrist, and there is a need for training in this regard. Future courses on genetic counselling would be extremely useful, as well as the involvement of genetic counsellors from African backgrounds.

The second part of the course that was particularly interesting to me was the coverage of family perspectives, communication, support and information. The importance of communities and patient advocates was nicely highlighted but unfortunately, such patient communities do not exist in all countries. The course emphasised the valuable role of patient advocates and how they can be useful, especially in my country where patients with some types of disease, including HD, are extremely stigmatised. As a result of the course, I came to understand my own role in supporting patients in communicating and advocating for their wellbeing.

Finally, the sections on pharmacological and non-pharmacological management were also very interesting and provided important updates on the management of HD. However, unfortunately, most of these interventions are not yet available in my country.

I thank the EHDN and the MDS for this wonderful provision and look forward to future courses on HD clinical care and research.

Photo: Shaimaa El-Jaafary

Shaimaa El-Jaafary

Shaimaa Ibrahim El-Jaafary, Associate Professor of Neurology at Cairo University in Egypt and previous EHDN-MDS Fellow, noted the importance of the course in decreasing the knowledge gap in HD.

As a clinical subspeciality, the study of movement disorders is not well characterised in either sub-Saharan Africa or Middle Eastern countries, and formal courses and fellowships are sadly lacking. When it comes to HD, the knowledge gap between Eastern and Western countries remains very wide, but this course represents an important step towards decreasing this gap. This well-structured course, delivered by eminent speakers, succeeded in giving us the chance to understand HD from different perspectives and allowed us to interact with the speakers. The discussions were extremely stimulating and also important for ensuring deeper exploration of key concepts and the tailoring of some interventions to our available resources.

Looking forward, we need to know more about conducting clinical research on HD, and how to set up national registries involving countries across Africa and the Middle East. It would be great if future courses could consider this perspective as well.

Photo: Emilia Sitek

Emilia Sitek

Emilia Sitek, Associate Professor, Medical University of Gdansk Poland, EHDN study site, St. Adalbert Hospital, Copernicus PL, Gdansk, Poland, appreciated the strong clinical focus of the course.

All the clinical speakers shared with the audience up-to-date research results and most importantly, their practical experience. The clinical lectures were easy to follow thanks to a variety of video examples and clear explanations. The course really emphasised the importance of multidisciplinary team working, showing how each specialty can contribute to patient management.

Professor Michael Orth (EHDN Science Director and of the University of Bern, Switzerland) provided a step by step demonstration of a short clinical examination focusing on motor symptoms. Professor Bernhard Landwehrmeyer (Ulm University, Germany) discussed not only motor function assessment, but also history taking, including the patient's and his/her family perspectives, and the clinical assessment of cognition and language in his practice with a focus on the qualitative interpretation of the Clock Drawing Test and a description of Cookie Theft picture. As a clinical neuropsychologist, I particularly appreciated hearing a movement disorder expert discussing the integration of behavioural neurology assessment into neurological examination. Of note, Bernhard Landwehrmeyer emphasised the necessity of adjusting assessment to the disease stage and strongly prioritised addressing functional impairment over motor dysfunction when planning the patient's management.

I was particularly impressed by the neuropsychiatric presentation given by Professor Hugh Rickards (Consultant in Neuropsychiatry Birmingham and Solihull Mental Health Foundation Trust, UK). I have attended several of his presentations at previous EHDN conferences, but it was the first time I heard him focus on the more clinical aspects of his work and the way he approaches patients and their families. His presentation touched upon two aspects that are very important in my research and clinical practice: poor insight in many HD patients and anticipatory grief in the family. When I did my PhD on anosognosia in HD, there were very few studies devoted to this topic and it was rarely discussed at conferences. I am very pleased that this problem is now fully acknowledged by movement disorders experts and that the need to discuss the patient's and the family's perspectives was emphasised by all clinical speakers. As far as family context is concerned, I appreciated the willingness and openness of Dr Jeff Carroll (Western Washington University, USA) in sharing his story. He remains a hero for many HD families.

As a lecturer, I will never forget the flamenco dance which was chosen as a starting point to define chorea by Michael Orth. I deeply admired the way he introduced the clinical phenotype, step by step, effectively moving from simple language to medical terminology to ensure audience comprehension.

• • •

Photo: Jenny Townhill

Photo: G. Stautner, Artifox.com

Update: Clinical Trials

Jenny Townhill and Tim McLean, Central Coordination

Jenny Townhill and Tim McLean, Central Coordination
The following studies have been endorsed by EHDN. Endorsement of a study protocol follows review by the EHDN SBAC (see the article 'The Scientific and Bioethics Advisory Committee – Our Responsibilities and Challenges' in this edition), which makes its recommendations to the EC. If endorsed, a formal letter of endorsement is then issued to the study sponsor, allowing them to inform relevant regulatory authorities and/or ethics committees that the study protocol has been reviewed and endorsed by a group of expert HD scientists and clinicians. The endorsement may also be posted on the EHDN website, signalling the same message to the HD community.

Key updates are provided below for the EHDN endorsed trials and studies that are active or in start-up; please refer to Table 1 for a summary of the main study information.

NOVARTIS

VIBRANT-HD (Novartis)

Recruitment has started for this global multicentre Phase IIb trial of branaplam in Stage I and Stage II participants with HD. The main aim of the trial is the assessment of safety and tolerability and identifying a dose of branaplam that lowers mutant huntingtin to a level that would predict clinical benefit following 16 weeks of treatment.

SOM BIOTECH

SOM3355 (SOM Biotech)

This study, exploring the efficacy and safety of SOM3355 (bevantolol) in treating chorea, is currently in start-up at approximately 20 sites in Europe, with recruitment anticipated to start early in 2022.

WAVE LIFE SCIENCES

SELECT-HD (Wave Life Sciences)

Recruitment continues for the Phase Ib/IIa SELECT-HD trial of the allele selective ASO WVE-003. The study is running at multiple sites in Europe and Canada and is open to people with early-manifest HD who carry a specific single-nucleotide polymorphism.

GENERATION-HD1 and GENEXTEND (Roche)

See the article 'What's Next for the Tominersen Development Programme?' in this edition for a summary of the results to date.

HD-DBS (Heinrich-Heine University, Düsseldorf)

This multicentre trial exploring the safety and efficacy of deep brain stimulation in 48 people with HD completed recruitment in 2021, with the last patient visit in December 2021. Data analysis is underway and results are expected during 2022.

DOMINO-HD (Cardiff University)

Recruitment into this study exploring digital technologies will close in March 2022. Study timelines and recruitment have been significantly impacted by COVID-19 restrictions.

PROOF-HD (Prilenia Therapeutics)

Recruitment was completed into this global Phase III trial of pridopidine ahead of schedule and slightly over the enrolment target of 480 patients in October 2021. The aim of the study is to evaluate the effect of pridopidine, an oral drug candidate, on total functional capacity. Following completion of the double-blind period, all participants have the option to enrol into an open-label extension. Results are expected in IQ2023.

HDGeneTRX2/AMT-130-2 (UniQure)

This European gene therapy trial of AMT-130 in people with early manifest HD initiated screening in December 2021. The study is planned to be conducted in Poland, the UK and Germany.

Table 1: EHDN-endorsed Trials and Studies

(Active or in Start-up)

Registration ID (CT.gov)	Sponsor	Trial name	Phase	Intervention	Mechanism of Action	Target Enrolment	Location(s)	Status
N/A	Cardiff University	DOMINO-HD	N/A	N/A	N/A	300	Poland, Spain, Switzerland, UK	Recruiting
NCT02535884	Heinrich-Heine University, Duesseldorf	HD-DBS	II	Deep brain stimulation	High-frequency stimulation of the Globus Pallidus	50	Austria, Germany, Switzerland	Completed
NCT05111249	Novartis	VIBRANT-HD	IIb	LMI070/branaplam	Small molecule mRNA splicing modifier	75	USA, Canada, Europe	Recruiting
NCT04556656	Prilenia Therapeutics	PROOF-HD	III	Pridopidine	Sigma-1 receptor agonist	480	USA, Canada, Europe	Participant follow-up
NCT03842969	Roche	GEN-EXTEND	OLE	RG6042/tominersen	Allele-nonselective ASO	1,100	USA, Canada, Europe	Participant follow-up
NCT03761849	Roche	GENERATION-HD1	III	RG6042/tominersen	Allele-nonselective ASO	801	Australasia, Canada, Europe, Japan, USA, Latin America	Participant follow-up
TBD	SOM Biotech	SOM3355	IIb	SOM3355/bevantolol	VMAT2 inhibition	129	Europe	In start-up
NCT04406636	Triplet Therapeutics	SHIELD-HD	N/A	N/A	N/A	60	USA, Canada, Europe	Participant follow-up
NCT04120493	UniQure	HD GeneTRX2/AMT-130-02	Ib/II	rAAV5-miHTT	miRNA nonselective (gene therapy)	26	UK, Germany, Poland	In start-up
NCT05032196	Wave Life Sciences	SELECT-HD	Ib/IIa	WVE-003	Allele-selective ASO	36	Australia, Canada, Europe	Recruiting

Note. ASO = antisense oligonucleotide; OLE = open-label extension; VMAT2 = vesicular monoamine transporter 2


Photo: G. Stautner, Artifox.com

Update: Enroll-HD – An Opportunity for Nested Studies

Olivia Handley, Enroll-HD Global Platform Manager

This year will mark the 10th anniversary of Enroll-HD. With over 27,000 participants and its expanding capacity to support a wide range of clinical trials and studies via an extensive network of sites and investigators, Enroll-HD continues to successfully deliver on its goal to serve as a clinical research platform for HD.

One specific way in which the platform can be leveraged is to 'nest' Enroll-HD with other studies. Through careful planning and consultation with the Enroll-HD team, study teams can design their protocols to link with the Enroll-HD visit schedule. This allows Enroll-HD participants co-participating in nested studies to share their Enroll-HD data. Not only does this approach significantly reduce participant burden, but it also decreases the resources required of sites. The design means there will be fewer and/or shorter study visits along with access to experienced HD clinical sites often with a large, well-characterised participant cohort. It also minimises the potential for practice effects (e.g., in cognitive assessments) by removing unnecessary duplication of assessments.

Here we briefly describe the CHDI-funded study Later Stage HD Assessments (LSA) and how it is nested with Enroll-HD.

Study overview: As HD progresses, participants become increasingly dependent on caregivers and attendance at annual study visits becomes more difficult. Additionally, participant-completed assessments that require motor or verbal responses may no longer be practical (as evidenced by increasing missing data) or valid (e.g., cognitive assessments). Therefore, there is a need to develop remotely delivered clinimetrically sound companion-report measures of HD-relevant domains.

The LSA study aims to develop two informant report measures: (1) Structured Interview of Function (HD-SIF) and (2) Huntington's Disease Clinical Status Questionnaire (HDCSQ).

Design: The study will recruit approximately 170 HD participants who are in mid- to later stages of HD and their companions, and is comprised of two parts:

- Part 1 will evaluate the reliability and validity of the HD-SIF (N = 20 HD individuals and their companions)
- Part 2 will assess the clinimetric properties of the HD-SIF and HDCSQ (N = 150 HD individuals and their companions)

Nesting with Enroll-HD: HD participants must be participants in Enroll-HD. This enables the study to optimise the use of Enroll-HD data in two ways: 1) to identify potentially eligible participants based on data from their most recent Enroll-HD visit, and 2) to use key assessments from a combined Enroll-HD/LSA study visit. LSA is hosted on the centralised Enroll-HD electronic data capture (EDC) system, providing sites with full access and visibility of co-participating participants along with tools to help schedule combined study visits.

For further information on nesting studies with Enroll-HD please contact Olivia Handley, olivia.handley@enroll-hd.org.

Update: HD Clarity

Seema Maru, HDClarity Study Coordinator and Alex Lowe, HDClarity Research Assistant

HDClarity is an initiative designed to address the rapidly growing demand for cerebrospinal fluid (CSF) from well-characterised gene expansion carriers across the entire spectrum of HD.

Current Site Status

- The primary objective is to collect high-quality CSF from at least 2,500 participants for the evaluation of biomarkers and pathways that will enable the development of novel treatments for HD
- The secondary objective is to generate a high-quality plasma sample collection matching the CSF collections, which will also be used to evaluate biomarkers and pathways of relevance to HD research and development

Since 2016, HDClarity has opened across seven nations worldwide and has over 500 participants. Our current active sites are located across the UK, Canada, USA, Germany, Italy, Poland and Spain. We have sites commencing soon in Austria, Australia, France, Netherlands, Norway, New Zealand, Portugal and Switzerland. Recently, we have opened the study in new sites in the UK and Germany.

Total Recruitment

As of January 2022, HDClarity sites have successfully completed 657 sampling visits, including optional repeat, longitudinal and longitudinal repeat visits across all participant groups and have collected over 11 litres of CSF.

COVID-19 Recovery

One of the many casualties of the COVID-19 pandemic was the upheaval in global clinical research, with lockdown measures making it difficult for patients to attend site visits and many clinical staff being redeployed to treat critically ill patients. Consequently, ongoing studies were temporarily halted, and the establishment of new trials was paused around the world. Many patients were reluctant to participate in clinical studies due to a fear of infection, which was particularly significant among clinically vulnerable groups. As a result, slow enrolment and high dropout rates caused delays in planned and ongoing studies.

Despite these obstacles, HDClarity continued to recruit new participants and collect valuable biosamples at both baseline and longitudinal follow-up.

Initially, after one screening and sampling visit (with an optional repeat visit if applicable), a participant's role in the study is complete. However, the implementation of Protocol V3 provided participants with the option to consent to repeat the screening and sampling visit on an annual basis. This is termed a longitudinal visit and participants are free to choose whether they would like to attend these visits.

Obtaining data and biosamples from longitudinal visits provides valuable insight into the dynamics and prognostic potential of biomarkers derived from plasma and CSF. The team at University College London and CHDI encourage sites to prioritise these visits when possible, as they are of critical importance to understand how the biomarker under study relates to disease progression. Such visits have already been conducted in Canada, Germany, Italy and the USA.

The Future

Since HDClarity began in 2016, it quickly became apparent that there was a growing demand for high-quality CSF and plasma samples for research on novel therapies and the validation of biomarkers. For this reason, Protocol V3 was amended to expand the study significantly at all participating sites.

The HDClarity team were delighted to receive UK ethics approval for Protocol V4.1. In addition to introducing

and opening the study to as many Enroll-HD sites as possible, the team are also prioritising the transition of current HDClarity sites onto the new protocol. The study will now include:

- Four Annual Screening and Sampling Visits (i.e., at 1, 2, 3 years after the first initial visit), after which participants can consent to take part again
- Recruitment target has been increased from 1,200 to 2,500 participants
- Minimum age for controls and participants with pre-manifest disease has been reduced from 21 to 18 years
- Addition of two new participant cohorts:
  Juvenile manifest HD
  HD participants with a huntingtin gene cytosine-adenine-guanine (CAG) of 36-39 repeats

The protocol and further information are available at www.hdclarity.net and the study team, led by Professor Ed Wild are always happy to answer any questions.

Finally, we would like to thank all the study volunteers and clinical research facilities who have given their time, dedication, and commitment to HDClarity. Your continued support has been invaluable and directly contributes to the studies success.

For more information and details on participating in HDClarity, please email hdclarity-cc@enroll-hd.org.

• • •

EHDN News
EUROPEAN HUNTINGTON'S DISEASE NETWORK

Thank You for Your Feedback!

In 2021, we conducted reader/user surveys of EHDN *News* and our web pages. We are very grateful to all those who took part and shared their valuable suggestions. Your feedback means a lot to us – and remember, you can contact us at any time with comments and ideas (newsletter@euro-hd.net).

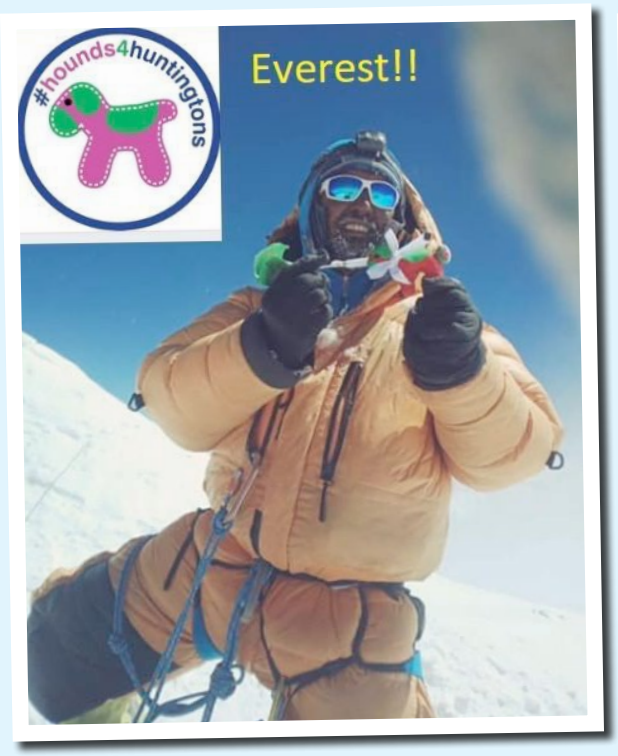
Photo: Kindly provided by Annelien Duits

Annelien Duits

Update: New Seed Funds Awarded

The EHDN has recently awarded seed funding to Annelien Duits at Maastricht University for an exciting new project titled 'Huntington Partner in Balance: Online Self-management for Partners/Caregivers of Persons with Huntington Disease'. Overburdening the caregiver can lead to anxiety and depression and ultimately, to the inability to maintain their informal role in the treatment of HD. It is therefore of great importance to preventively increase the resilience of caregivers, and in this way, prevent overloading at a later stage of the care process. This project aims to develop and evaluate an online self-management program for partners, relatives and caregivers of HD patients. This intervention will be based on the blended care self-management program Partner in Balance (PiB) for partners of patients with dementia, which has proven to be effective (partnerinbalans.nl/home/en/).

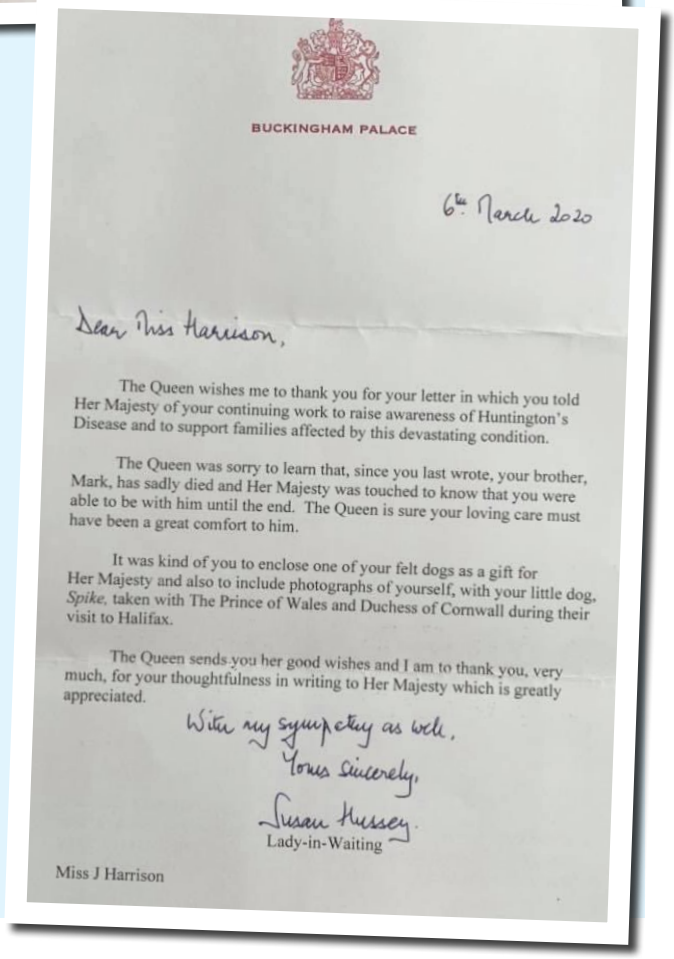
Seed funds are intended to support pilot studies that will eventually kickstart larger projects. The next deadlines for applications are 1 March 2022 and 1 November 2022. More information about the programme and how to apply can be found here or you can contact Christine Capper-Loup (Christine.Capper-Loup@siloah.ch) for further information.



Photos: Jackie Harrison

Send Us Your Photos!

Jackie Harrison (@jaq421 on Twitter) explains 'This effort is inspired by our much loved and missed border terrier, Sybil. I've made probably thousands of these small felt dogs and they travel the world sharing their adventures to raise awareness of HD. They've also raised thousands of pounds for the UK Huntington's Disease Association and the HDYO. People share photos on their social media and share them on the Sybil pages. This all started while I was caring for my brother in the late stages of HD. As a carer, it is impossible to travel but the project has connected me to people all over the world, including HD-affected families and those with no connection to the disease. One Sybil travelled to Everest with a Nepalese climber Wangda Sherpa and another went to the South Pole with Gregory Youdan! When people see a Sybil they often ask what it's about, so there's always an opportunity to tell people more about HD.'



BUCKINGHAM PALACE

6th March 2020

Dear Miss Harrison,

The Queen wishes me to thank you for your letter in which you told Her Majesty of your continuing work to raise awareness of Huntington's Disease and to support families affected by this devastating condition.

The Queen was sorry to learn that, since you last wrote, your brother, Mark, has sadly died and Her Majesty was touched to know that you were able to be with him until the end. The Queen is sure your loving care must have been a great comfort to him.

It was kind of you to enclose one of your felt dogs as a gift for Her Majesty and also to include photographs of yourself, with your little dog, *Spike*, taken with The Prince of Wales and Duchess of Cornwall during their visit to Halifax.

The Queen sends you her good wishes and I am to thank you, very much, for your thoughtfulness in writing to Her Majesty which is greatly appreciated.

With my sympathy as well,
Yours Sincerely,
Susan Hussey
Lady-in-Waiting

Miss J Harrison

Our photo experiment continues!

Whether you're affected by HD personally, or you're a carer, clinician or scientist working in the field, we'd like to publish your images in the newsletter. If you have a photo that provides an insight into your daily life that you think might interest or inspire other EHDN members – or make them think differently about the disease – please send it to us along with a few words explaining who you are and what the image shows: **newsletter@euro-hd.net**

Being 'Hidden No More': An Interview with Charles Sabine, OBE

Photo: Martin Sølyst

Charles and John Sabine

Award-winning journalist Charles Edward Sabine, OBE, is a leading global advocate for patients and families affected by degenerative brain disease and the founder of the Hidden No More Foundation. Charles was recently appointed an Officer of the Most Excellent Order of the British Empire by Her Majesty Queen Elizabeth II in the New Year's Honours List 2022. We were delighted to have the opportunity to speak with him about his inspiring and critical work in HD and beyond.

From covering the conflict in Iraq to the troubles in Belfast, you're a household name with a reputation for hard-hitting journalism. Could you start by telling us how you came to be involved with HD?

My father was one of the first people to be diagnosed with HD by genetic testing. At that time, I was working for the American news network known as the National Broadcasting Company (NBC), covering mostly wars and conflicts. When I heard about my father, it came completely out of the blue. And I discovered that this is often how it happens for many families, because the disease has been hidden so much and the lengths to which some families can go to hide it are extraordinary.

For my family, it could no longer be hidden. My father underwent genetic testing at Queens Square (University College London) by the predecessor of the neurologist and neuroscientist Sarah Tabrizi. Because it was positive, they had to fess up to me and my brother – and it was a complete and utter shock to us. We'd never heard of HD and had not only to learn about the nature of the disease and the symptoms but, even worse than that, its genetic nature. At that time, my brother John was a senior barrister working in the High Court. When he tested positive, he had already had three children.

I put off my test and continued my work at NBC. It was about 12 years later that I reached a stage in my life where I needed the empowerment of the knowledge that the test would provide. It was not long after testing positive that I realised that no one was speaking for this community or representing them. There were, of course, clinicians and so on, like Sarah Tabrizi, but there was no one who was actually gene-positive standing up. So, I decided to use my influence as a correspondent to open doors. I stopped working at NBC in 2007 and I've worked in HD ever since.

> *'Everything about the disease is made more difficult by the fact that people hide it away.'*

You mentioned that HD is often 'hidden'. What do you mean by that?

One of the things that I quickly discovered was that the prevalence of HD is massively underestimated. Everything about the disease is made more difficult by the fact that people hide it away. Around 80% of people don't get tested, so we just simply don't know how many people in the world have HD. The fact that people hide it away makes life worse, for individuals and for families, like it did my family.

I think my father shortened his life by having this horrible secret that he kept from everyone. My brother and I compare this to what I've done, which is to engage. Underestimating the true numbers of people with HD obviously affects research and funding. We also don't have as many people engaging in clinical trials as we should. This is a particular problem that I have engaged with increasingly and as part of this, set up an initiative in 2010 in the UK called 'Hidden No More'.

Hidden No More aims to empower and enable patients and families facing HD. In 2010, we launched an All-Party Parliamentary Group for HD in the UK. Under that banner, we held our first really big visual event in which around 700 people came from all over the country to dress up in green at Parliament Square in London.

In 2017, you met with Pope Francis, who became the first global leader to publicly recognise HD. How did this come about?

We were working with Elena Cattaneo, an HD researcher at the University of Milan, and she got us into the Vatican. All I had hoped for was to simply have the Pope stand with a scroll saying that HD should be hidden no more, the idea was similar to how we had taken a banner to the UK Parliament with the same message.

Photo: Kindly provided by Charles Sabine

Dancing at the Vatican by Charles Sabine

But Pope Francis went so much further than that, meeting hundreds of patients, carers and family members. One of these was Brenda, a 15-year-old girl from Buenos Aires who had not been able to go to school because the other parents didn't want their children 'catching' HD. When she was hugged by the Pope, this was a big, big moment. And this was all live on the Vatican TV. All around the world, the leader of our one and a quarter billion Catholics was heard to declare that Huntington's should be hidden no more.

> *'All around the world, the leader of the one and a quarter billion Catholics was heard to declare that Huntington's should be hidden no more.'*

My documentary, Dancing at the Vatican, tells the story of the brave families from Latin America who made the journey to that meeting. Dancing at the Vatican had a big premiere in Los Angeles in Hollywood and then we had a European premiere at the BAFTAs in London – it was all fantastic. While the COVID pandemic put stop to further premieres, we were able to release Dancing at the Vatican via YouTube and Amazon Prime. It's available in six languages and more people than ever are watching it – at any moment of any day, there are two screens showing that film somewhere in the world. It's the gift that keeps on giving and I'm so glad we got it out there before COVID struck.

That brings us on to your most recent film, The Hoping Machine. Can you tell us about this?

So, every year for the past 15 years, the CHDI Foundation has organised the Huntington's Disease Therapeutics Conference. Each year, individuals affected by the disease – many with no experience of public speaking – have stood up in front of hundreds of leading scientists and clinicians across the world to talk about their experiences as part of the opening keynote. Last year, I met with lots of these people via Zoom to hear their stories. It was really rewarding – there were lots of extraordinary, very different and unique stories but they were all imbued with the same courage and hope. This is why I called it The Hoping Machine, after the poem written by Woody Guthrie (the very famous American folk singer who died with HD).

We used bits of the poem in the film and one of the people we interviewed was his daughter.

I think, really genuinely, that The Hoping Machine is the best introduction you could have to HD research because it says so much about its uniquely collaborative feel. We are very lucky to have this amazing and unique collaboration in which everyone wants to find a treatment for the disease. This is true even for big pharma, which is typically very far removed from the patient experience.

'The carers are the real, true heroes in our community and so I'm sharing this with them.'

A real curveball, as the Americans would call it, was thrown at me when I'd been working on the film for several months, and that was the Roche announcement on the tominersen trials. I asked myself whether the interviews would still stand, and I watched all of it again, and realised I didn't need to change a single word. It all still stood.

All this work culminated in you being awarded an OBE at the end of 2021. This is such an amazing inspiration to us all. How do you feel about it?

It is indeed an extraordinary honour. Basically, a list comes out twice a year (once on the Queen's official birthday in the middle of the summer and the other one on New Year's Eve when people are told about their awards) and then the investiture happens. They're behind on this because of COVID, so it will probably be May or June when I go to the palace.

It is a fantastic honour but more importantly, as I said at the time, this is for way more than me. This is for all the people who've gone before, and those who do far, far greater work than I do. I've spent many years now doing what I do, but the one thing I've never been is a carer. The carers are the real, true heroes in our community and so I'm sharing this with them. HD has been associated with shame, criminality and stigma. My getting this award is another step towards breaking down this shame and stigma – HD is, after all, just a disease.

Further Resources

- *Hidden No More Foundation: hiddennomore.com*
- *Dancing at the Vatican: dancingatthevatican.com/charles-sabine*
- *The Hoping Machine: hiddennomore.com/initiatives*

• • •

Follow us on Twitter: @EHDN_News

In our next issue of EHDN News, we meet HDYO's founder and recent MBE recipient, Matt Ellison, and reflect on the importance of George Huntington's seminal paper, titled 'On chorea' and published almost 150 years ago, as we look towards our 2022 Plenary Meeting.

Dates for your diary

- The Huntington's Disease Youth Organization's **International Young Adults Virtual Congress** takes place 5–6 March 2022. Registration is free. Click here for more details.
- The UK Huntington's Disease Association is holding a **pre-implantation genetic diagnosis event for young adults** on Thursday 7 March 2022. Find out more and register here.
- The MDS-European Section is inviting participants for their **2022 regional education courses** including the Clinical Neuropsychiatry of Movement Disorders. Details of all courses can be found here.
- The Huntington's Disease Society of America's **37th Annual Convention** takes place 9–11 June 2022 in Atlanta. Click here for details.
- The EHDN Plenary Meeting will take place in **Bologna, Italy,** 16–18 September 2022. Registration and abstract submission will open in May 2022.

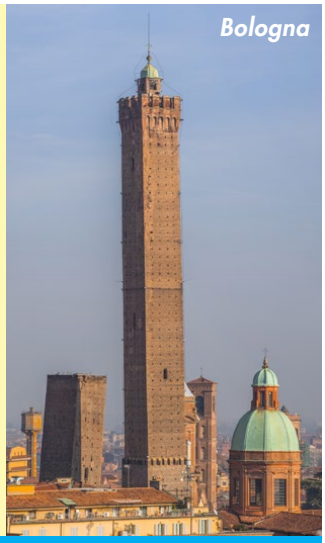


Photo: © Convention Bureau Italia S.C.R.L.

Would you like to share an upcoming event with our readers? Please email the details to newsletter@euro-hd.net